(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 April 2002 (18.04.2002)

PCT

(10) International Publication Number
WO 02/30895 A1

(51) International Patent Classification[7]: C07D 209/42, 491/04, 413/12, 409/04, 405/04, 417/04, 405/10, 401/12, 405/12, A61K 31/404, 31/428, 31/423, 31/343 // (C07D 491/04, 317:00, 209:00)

(21) International Application Number: PCT/US01/42644

(22) International Filing Date: 9 October 2001 (09.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/239,195 10 October 2000 (10.10.2000) US

60/243,665 27 October 2000 (27.10.2000) US

(71) Applicant: BAYER CORPORATION [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US).

(72) Inventors: **STOLLE, Andreas**; Carl-Duisberg-Strasse 310, 51373 Leverkusen (DE). **DUMAS, Jacques, P.**; 98 Farmview Road, Bethany, CT 06524 (US). **CARLEY, William**; 7946 Prospect Place, La Jolla, CA 92037 (US). **COISH, Phillip, D., G.**; 548 Orange Street, Suite 401, New Haven, CT 06511 (US). **MAGNUSON, Steven, R.**; 124 Kimberly Avenue, Hamden, CT 06518 (US). **WANG, Yamin**; 10 Russet Road, Sandy Hook, CT 06482 (US). **NAGARATHNAM, Dhanapalan**; 52 Virginia Rail Road, Bethany, CT 06524 (US). **LOWE, Derek, B.**; 31 Bittersweet Lane, Hamden, CT 06518 (US). **SU, Ning**; 121 October Hill Road, Hamden, CT 06518 (US). **BULLOCK, William, H.**; 60 Herrmann Lane, Easton, CT 06612 (US). **CAMPBELL, Ann-Marie**; 69 Lynn Drive, Monroe, CT 06468 (US). **QI, Ning**; 109 Kaye Vue Dr. 1E, Hamden, CT 06514 (US). **BARYZA, Jeremy, L.**; 945 High School Way, Apt. #19, Mountain View, CA 94041 (US). **COOK, James, H.**; 174 Young Street, East Hampton, CT 06424 (US).

(74) Agents: **GREENMAN, Jeffrey, M.** et al.; Bayer Corporation, 400 Morgan Lane, West Haven, CT 06516 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/30895 A1

(54) Title: SUBSTITUTED INDOLES, PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH INDOLES AND THEIR USE AS PPAR-γ BINDING AGENTS

(57) Abstract: Disclosed are substituted indoles, pharmaceutical compositions containing such indoles, and their use in treating or preventing PPAR-γ mediated diseases or conditions, such as osteopenia, osteoporosis, cancer, diabetes and atherosclerosis.

Substituted Indoles, Pharmaceutical Compositions Containing Such Indoles and Their Use as PPAR-γ Binding Agents

Field of the Invention

The invention relates to substituted indoles, pharmaceutical compositions containing such indoles, and their use in treating or preventing diseases or conditions mediated by the Peroxisome Proliferator Activated Receptor-γ (PPAR-γ).

Background

Peroxisome Proliferator Activated Receptors (PPARs) belong to the steroid/retinoid receptor superfamily of ligand-activated transcription factors. Willson, *et al.*, Curr. Opin. Chem. Biol., (1997), Vol. 1, pp 235-241. To date, three mammalian PPARs have been identified, namely PPAR-α, PPAR-γ, and PPAR-δ.

PPARs regulate expression of target genes by binding to DNA response elements as heterodimers with the retinoid X receptor. These DNA response elements have been identified in the regulatory regions of a number of genes encoding proteins involved in lipid metabolism and energy balance. The biological role of the PPARs in the regulation of lipid metabolism and storage has been recently reviewed. Spiegelman, Diabetes, (1998), Vol. 47, pp. 507-514; Schoonjans, *et al.*, Curr. Opin. Lipidol., (1997), Vol. 8, pp 159-166; Brun, *et al.*, Curr. Opin. Lipidol., (1997), Vol. 8, pp 212-218.

Molecules that interact with PPAR-γ may be useful in modulating PPAR-γ mediated processes for the treatment or prevention of various diseases and conditions. For example, essential dietary fatty acids and certain of their eicosanoid metabolites are naturally occurring hormonal ligands for the PPAR-γ receptor, which can promote adipogenesis through activation of the PPAR-γ receptor. Kliewer, *et al.*, Proc. Natl. Acad. Sci. USA, (1997), Vol. 94, pp 4318-4323; Kliewer, *et al.*, Cell, (1995), Vol. 83, pp 813-819. Therefore, molecules that inhibit the adipogenic effects of endogenous PPAR-γ hormones may be useful in the treatment of diseases caused by increased fat accumulation or lipid storage, such as osteoporosis, obesity and acne. Tontonoz, *et al.*, Curr. Opin. Genet. Dev., (1995), Vol. 5, pp 571-576. For example, it has been noted that the

thiazolidinedione (TZD) class of PPAR-γ ligands promotes adipogenesis in bone marrow and inhibits expression of markers of the osteoblast phenotype, such as alkaline phosphatase. Paulik, *et al.*, Cell Tissue Res., (1997), Vol. 290, pp 79-87. These effects may lead to low bone mineral density and osteoporosis. Similarly, it is known that TZDs can promote lipid accumulation in sebocytes. Rosenfield, *et al.*, N. Dermatology, (1998), Vol. 196, pp 43-46. These effects may lead to sebocyte differentiation and acne formation. Thus, molecules that block adipogenesis in adipocytes, pre-adipocytes, bone marrow, or sebocytes may have beneficial effects in the treatment of obesity, osteoporosis, or acne.

The PPAR-γ receptor has been found in tissues other than adipose, and it is believed that synthetic PPAR-γ ligands and natural PPAR-γ hormones (natural ligands) may have beneficial effects in many other diseases including cardiovascular disease, inflammation, and cancer. Schoonjans, *supra*; Ricote, *et al.*, Nature, (1998), Vol. 391, pp 79-82; Mueller, *et al.*, Mol. Cell, (1998), Vol. 1, pp 465-470.

TZD PPAR-γ ligands enhance the actions of insulin in man and reduce circulating glucose levels in rodent models of diabetes. The PPAR-γ receptor is expressed in adipose tissue and plays a pivotal role in the regulation of adipocyte differentiation *in vitro*. TZD such as rosiglitazone induce adipocyte differentiation *in vitro* through activation of the PPAR-γ receptor.

Although there are clearly therapeutic uses for PPAR-γ ligands in the treatment of diseases of lipid metabolism and energy balance, it is possible that there will be side effects of these drugs. For example, PPAR-γ ligands that promote adipocyte differentiation *in vivo* could lead to increased fat accumulation and weight gain. This side effect might offset the beneficial effects of a PPAR-γ ligand in the treatment of diabetes or other diseases where obesity is a risk factor. Spiegelman, *supra*; Brun, *supra*.

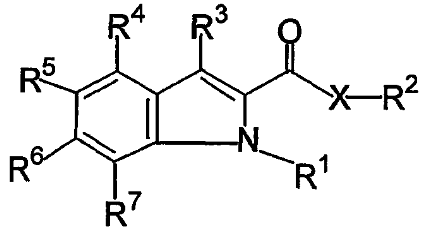
There is precedent among other member of the steroid/retinoid receptor superfamily that synthetic ligands can be identified which mimic many of the beneficial effects but inhibit some of the detrimental side effects of the natural hormones. McDonnell, Biochem. Soc. Trans., (1998), Vol. 26, pp 54-60. These synthetic ligands have been given various labels, including antagonists, anti-hormones, partial agonists, selective receptor modulators, tissue selective ligands, and others. Katzenellenbogen, *et*

al., Mol. Endocinol., (1996), Vol. 10, pp 119-131. Compounds are needed that will modulate PPAR-γ mediated processes for the treatment or prevention of diseases such as osteoporosis, cancer, *etc.* without the concommitant side-effects of natural hormones.

Summary of the Invention

The invention provides compounds that modulate PPAR-γ mediated processes, particularly substituted indole compounds, which can act as agonists or antagonists of PPAR-γ and thereby modulate PPAR-γ mediated processes. The invention further provides pharmaceutical compositions containing such compounds. Finally, the invention provides for methods of treating or preventing a PPAR-γ mediated diseases or condition in a mammal by administering a compound of the invention.

The invention relates to compounds of the Formula I:



(I)

wherein

R^1

is R^8-R^9;

R^8

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $(CH_2)_tS(=O)_2$, and $(CH_2)_nC(=O)$;

t

is 1-7;

n

is 0-8;

R^9

is selected from phenyl, cycloalkyl of 3-8 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^9 may be substituted with alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, halogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or $Q\text{-}(CH_2)_nR^{10}$;

Q

is selected from NR^{33}, NH, S and O;

R^{10}

is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

R^{33}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 1-8 carbon atoms and alkynyl of 1-8 carbon atoms;

X

is selected from NR^{33}, NH, O, and S;

R^2

is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, and $(CH_2)_nS(=O)_2R^{11}$;

R^{11}

is selected from aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, with the proviso that R^{11} is not isoxazole,

wherein R^{11} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

R^3

is selected from:

(a) R^{12}-R^{13}, wherein

R^{12}

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, and C(=O), and

R^{13}

is selected from cycloalkyl of 3-7 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{13} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; or

(b) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

all of which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, or may be spiro fused with cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-8 carbon atoms and 1-2 heteroatoms selected from N, S and O; or

(c) aryl of 5-14 carbon atoms or heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which are substituted with 1-3 of the following:

(i) $Si(CH_3)_3$;

(ii) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(iii) $S(=O)_2R^{14}$

wherein R^{14} is selected from cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(iv) R^{15},which combines with R^5 to form a radical of the formula $-Y-(CH_2)_t-$

Y-,

wherein Y is selected from NR^{33}, NH, S and O;

(v) $C(=O)R^{16}$,

- wherein R^{16} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and Z-R^{17},

- wherein Z is selected from $(CH_2)_n$, NH, NR^{33}, O and S,

- wherein R^{17} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(vi) Z-R^{18}-R^{19}, wherein:

- R^{18} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms, heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and $(CH_2)_nC(=O)$, and

R^{19} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of

3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, R^{20}-R^{21} and Z-R^{21}, and

- Z is as defined above, and
- R^{20} is selected from aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- R^{21} is selected from hydrogen, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

with the proviso that when R^3 is furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl R^3 may be unsubstituted, and

with the further proviso that, (1) when R^3 is aryl or heteroaryl, Z is O or $(CH_2)_n$, R^{18} is $(CH_2)_nC(=O)$, alkyl, aryl or heteroaryl, and R^{19} is hydrogen, halogen, haloalkyl or alkyl, or (2) when R^3 is phenyl or napthyl and R^{16} is alkyl, one of the following applies:

- R^5 is other than hydrogen and R^{23} is other than alkyl or alkenyl,
- X is NH and R^2 is $(CH_2)_nS(=O)_2R^{11}$,
- R^8 is $(CH_2)_nC(=O)$, $(CH_2)_tS(=O)_2$, alkenyl or alkynyl,
- R^9 is substituted with $Q(CH_2)_nR^{10}$,
- R^7 is other than hydrogen, or

- R^4 is other than hydrogen; and

(d) furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl, which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; or

R^4

is selected from hydrogen and E-R^{34}-R^{35},

wherein

E is selected from NR^{33}, NH, S and O;

R^{34} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

R^{35} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O; and

R^{33} has the meaning given above;

R^5

(1) is selected from:

(a) hydrogen;

(b) $(CH_2)_qCOOH$

where q is 1-4

(c) $C(=O)R^{22}$,

wherein R^{22} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(d) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(e) $-(CH_2)_n$-D-R^{23}, wherein:

(i) D is selected from NR^{33}, NH, S and O, and

(ii) R^{23} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $C(=O)R^{24}$, and $(CH_2)_mR^{24}$, wherein

- m is 0-4, with the proviso that when R^3 is phenyl or napthyl, Z is O, R^{18} is alkyl and R^{19} is hydrogen, halogen, haloalkyl or alkyl, m is 1-4,

- R^{24} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, C(=O)OH, NHR^{27}-R^{28}, NR^{27}-R^{28}, $(CH_2)_nOR^{27}$-R^{28}, NH-R^{29}-$R^{30}$and R^{29}-R^{30},

- R^{27} is alkyl of 1-8 carbon atoms,

- R^{28} is selected from hydrogen, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

- R^{29} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms, and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

- R^{30} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and C(=O)OH, or

(2) R^5 combines with R^6 to form a radical of formula -Y-$(CH_2)_t$-Y-,

wherein Y is as defined above;

R^6

is selected from hydrogen, OH, and T-R^{18}-R^{19},

wherein T is selected from NR^{33}, NH, S and O and R^{18}, R^{19} and R^{33} are as defined above;

R^7

is selected from hydrogen, $C(=O)R^{22}$, $(CH_2)_n$-D-R^{23}, and R^{31}-R^{32},

wherein D, R^{22} and R^{23} are as defined above, and

R^{31}

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and C(=O), and

R^{32}

is selected from aryl of 5-14 carbon atoms, heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

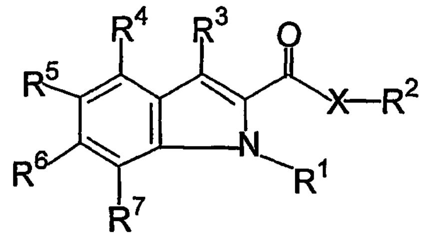
wherein R^{32} may be substituted with alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

and pharmaceutically acceptable salts thereof.

The invention further relates to pharmaceutical compositions containing any of the above-described compounds of Formula I and a pharmaceutically acceptable carrier.

The invention also provides methods for treating or preventing a PPAR-γ mediated disease or condition in a mammal. The PPAR-γ mediated disease or condition may be osteopororsis, osteopenia, PPAR-γ mediated cancer, including breast, prostate, colon and lung cancer, inflammation, including atherosclerosis, inflammatory bowel disease, Alzheimer's disease and rheumatoid arthritis, hypertension, hyperglycemia, type 1 diabetes, type 2 diabetes, syndrome X, insulin resistance, obesity, dyslipidemia, hypertriglyceridemia, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, and skin disorders, such as acne, psoriasis, dermatitis, eczema, keratosis and inflammatory skin

conditions caused by lupus erythematosus. The methods of the invention provide for the administration of a compound of Formula I or a compound of Formula IIa:



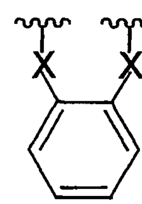
(IIa)

wherein

R^1

(1) is selected from hydrogen and R^8-R^9, or

(2) combines with R^7 to form a radical of the formula



R^8

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $(CH_2)_nS(=O)_2$ and $(CH_2)_nC(=O)$;

R^9

is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

wherein R^9 may be substitituted with alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, halogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or X-$(CH_2)_nCH_3R^{10}$,

R^{10}

is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

X and X′

are each independently selected from NH, NR^{33}, $(CH_2)_n$, O and S;

n

is a number from 0-8;

R^{33}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms and alkynyl of 2-8 carbon atoms;

R^2

is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, $NHS(=O)_2R^{11}$, and $(CH_2)_nS(=O)_2R^{11}$;

R^{11}

is selected from aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{11} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

R^3

is selected from:

(a) hydrogen,

(b) R^{12}-R^{13}, wherein

R^{12}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and $(CH_2)_nC(=O)$,

R^{13}

is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{13} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

(c) cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, all of which may be:

(i) substituted with aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and $C(=O)(CH_2)_nCH_3$, or

(ii) fused with a spiro ring of 1-6 carbon atoms, or

(iii) fused with an aryl of 5-14 carbon atoms or a heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, either of which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

(d) aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, either of which may be substituted with:

(i) $-Si(CH_3)_3$;

(ii) $S(=O)_2R^{14}$,

wherein R^{14} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(iii) R^{15}, which combines with R^5 to form a radical of the formula $-Y-(CH_2)_n-Y-$,

wherein Y and n are as defined above;

(iv) $C(=O)R^{16}$,

- wherein R^{16} is selected from alkyl of 1-8 carbon atoms and $X-R^{17}$
- wherein R^{17} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- wherein X is as defined above;

(v) $X-R^{18}-R^{19}$

- R^{18} is selected from alkyl of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

- R^{19} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, R^{20}-R^{21} and X-R^{21},
- X is as defined above,
- R^{20} is aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- R^{21} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

R^4

is selected from hydrogen and X-R^{18}-R^{19},

wherein X, R^{18} and R^{19} have the meanings given above;

R^5

(1) is selected from:

(a) hydrogen;

(b) R^{12}-R^{13},

wherein R^{12} and R^{13} are as defined above,

(c) $C(=O)R^{22}$, wherein

R^{22} is selected from alkyl of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(d) alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(e) $-(CH_2)_n$-Y-R^{23}, wherein:

(i) Y and n are as defined above,

(ii) R^{23} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $C(=O)R^{24}$, $(CH_2)_nR^{24}$, and R^{25}-R^{26}, wherein

- R^{25} is alkyl of 1-8 carbon atoms,
- R^{26} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

- R^{24} is selected from cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, C(=O)OH, NHR^{27}-R^{28}, NR^{27}-R^{28}, $NR^{33}R^{27}$-R^{28}, $(CH_2)_nR^{27}$-R^{28}, and R^{29}-R^{30},

- R^{27} is alkyl of 1-8 carbon atoms,

- R^{28} is selected from hydrogen, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, all of which, with the exception of hydrogen, may be fused with aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected N, S and O,

- R^{29} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

- R^{30} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of

5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(2) combines with R^6 to form a radical of the formula $-Y-(CH_2)_n-Y-$,

wherein Y and n have the meanings given above;

R^6

is selected from hydrogen, OH and $X-R^{18}-R^{19}$,

wherein X, R^{18} and R^{19} have the meanings give above

R^7

is selected from hydrogen, $C(=O)R^{22}$, $(CH_2)_n-Y-R^{23}$, and $R^{12}-R^{13}$,

wherein R^{22}, R^{23}, R^{12}, R^{13}, Y and n have the meanings give above;

and pharmaceutically acceptable salts thereof.

The present invention therefore provides compounds, pharmaceutical compositions containing such compounds, and methods for the treatment or prevention of PPAR-γ mediated diseases and conditions. Compounds, compositions and methods of the present invention therefore are useful in treatment of PPAR-γ mediated diseases and conditions without the concommitant undesired side-effects of natural hormones. These and other aspects of the invention will be more apparent from the following description and claims.

Detailed Description of the Invention

The invention provides novel, substituted indoles of Formula I, pharmaceutical compositions containing such indoles, and their use in the treatment or prevention of PPAR-γ mediated diseases or conditions in a mammal. The invention further provides methods of treating or preventing PPAR-γ mediated diseases or conditions in a mammal, such as a human, by administration of a compound of Formula IIa. The compounds of Formula I and Formula IIa have both been broadly described above.

In one embodiment of the compounds of Formula I:

R^8 is alkyl

R^9 is phenyl, which may or may not be substituted;

X is O;

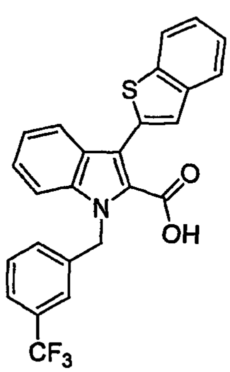
R^2 is hydrogen; and

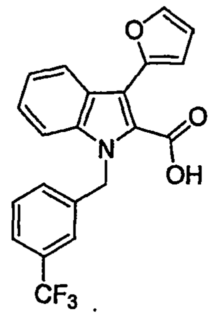
R^3 is aryl, particularly phenyl, or heteroaryl, either of which may or may not be substituted.

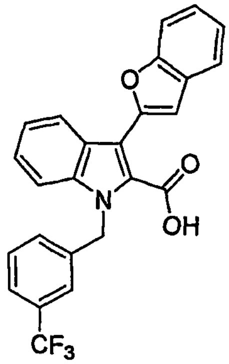
As used herein, the term "aryl" includes aromatic ring structures that are substituents on another atom. These aryls may also be substituted with substituents, such as halogen, haloalkyl, alkoxy, haloalkoxy, *etc.* Non-limiting examples of aryls include phenyl, napthyl, *etc.* Likewise, the term "heteroaryl" as used herein includes aromatic ring structures containing between one and two heteroatoms, such as O, N and S, that are substituents on another atom. These heteroaryls may also be substituted with substituents, such as alkyl, alkenyl, alkoxy, haloalkoxy, halogen, haloalkyl, *etc.* Non-limiting examples of heteroaryls include pyridyl, furyl, quinolyl, *etc.*

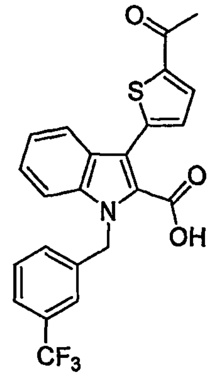
As used herein the term "alkyl" includes straight-chain or branched alkyls of between 1 and 8 carbon atoms. The term "alkenyl" includes straight-chain or branched alkenyls of between 2 and 8 carbon atoms. As used herein the term "alkynyl" includes straight-chain or branched alkynyls of between 2 and 8 carbon atoms. Such alkyls, alkenyls and alkynyls may be terminal or may be linkers between other portions of a molecule.

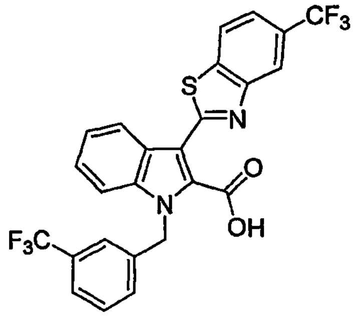
Examples of compounds of the invention where R^3 is a heteroaryl include, but are not limited to:

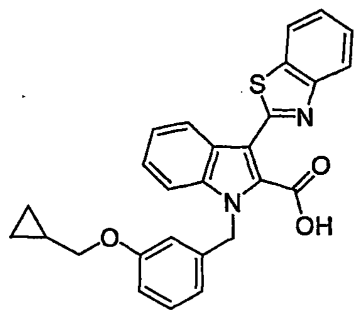


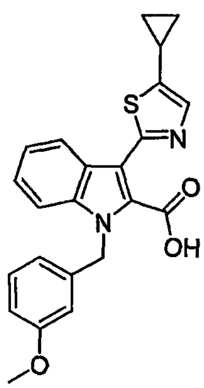


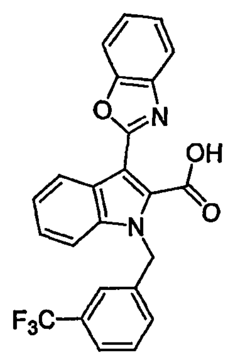


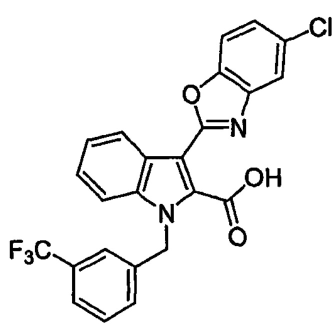


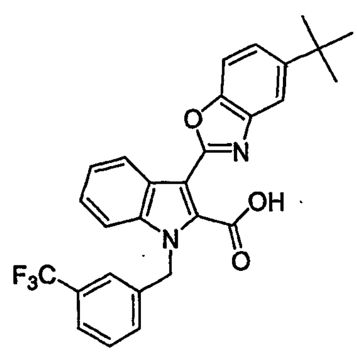


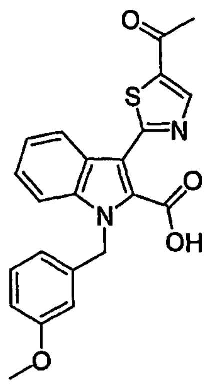




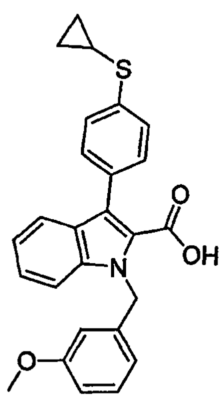


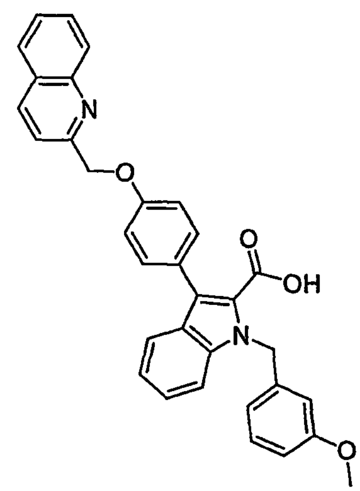


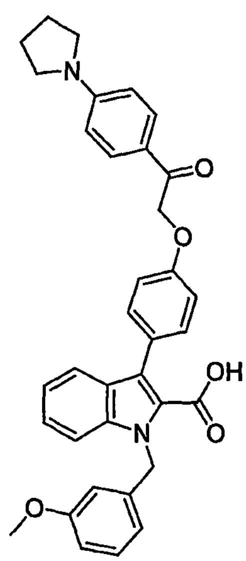


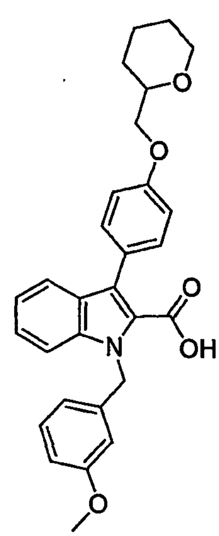


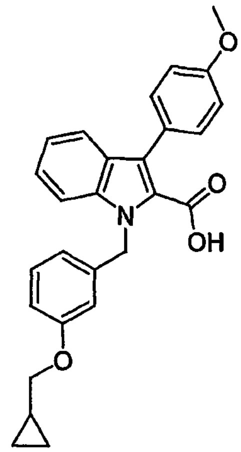
Examples of compounds of the invention where R^3 is phenyl include, but are not limited to:

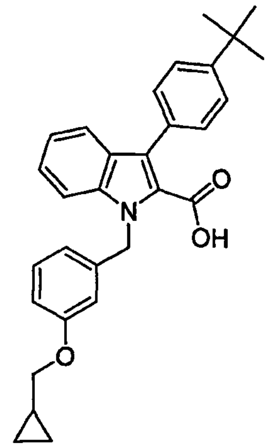


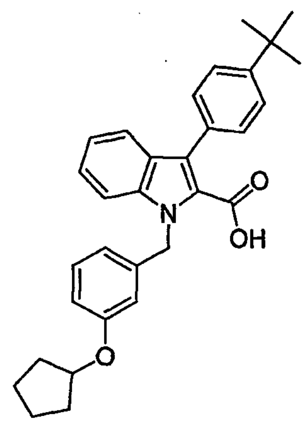


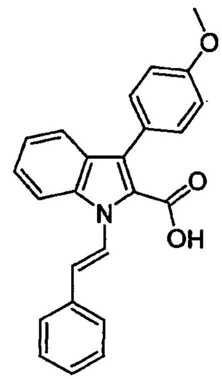


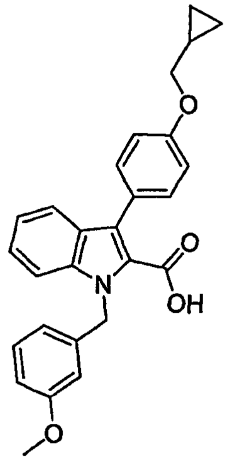


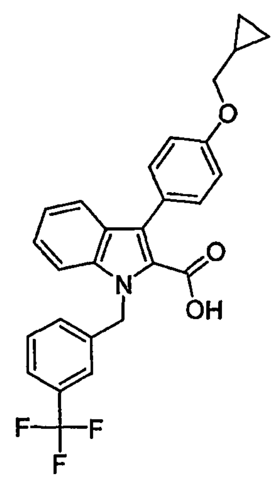

O
N
O
OH
O

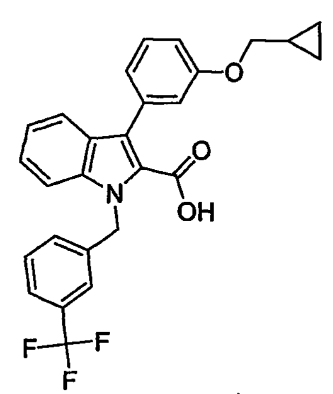

N
O
OH
O

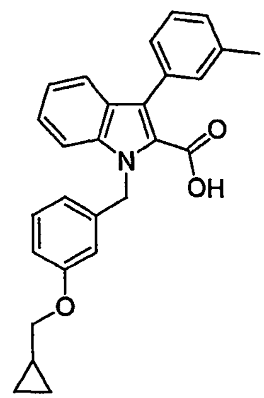

N
O
OH
O

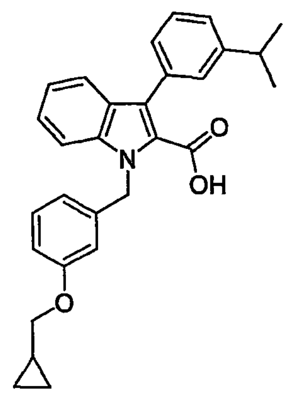

O
N
O
OH

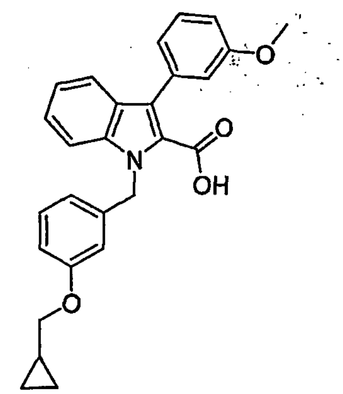

O
N
O
OH
O

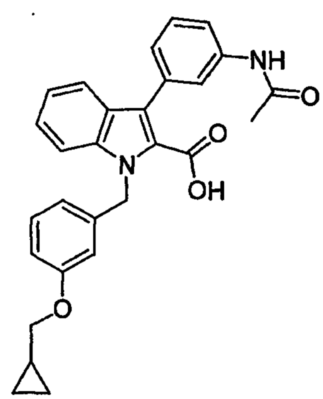

O
N
O
OH
F
F
F

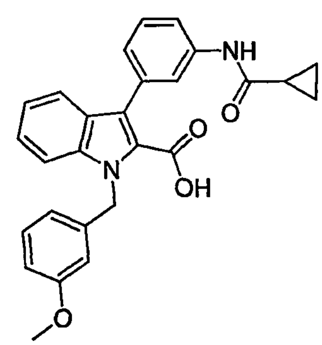


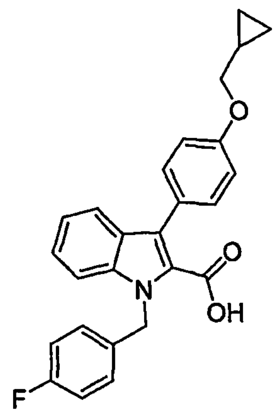


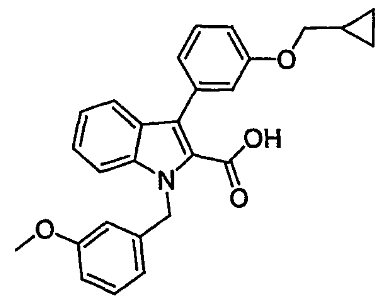


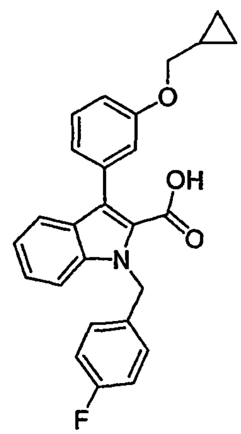


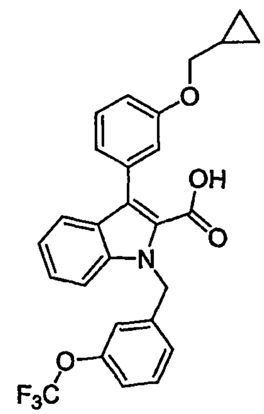


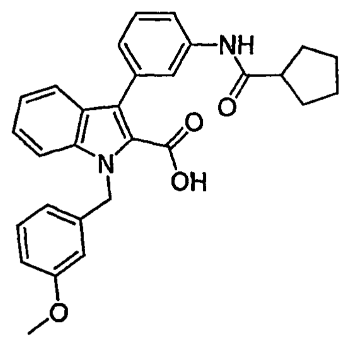


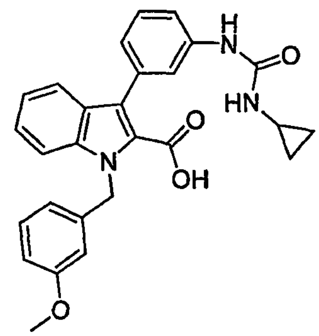


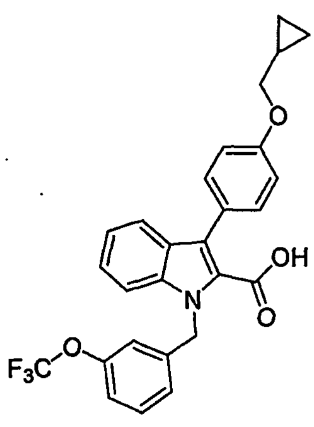


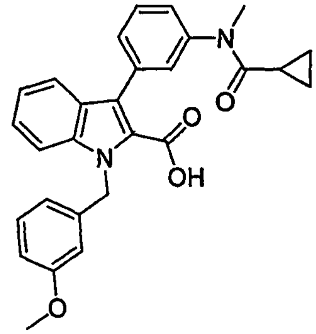


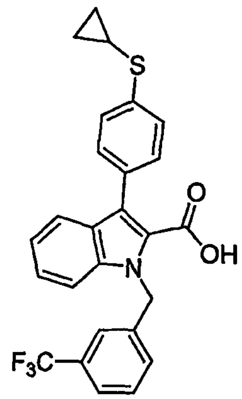




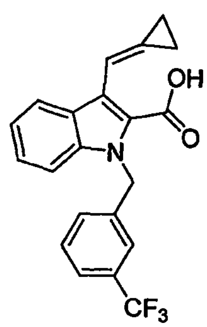


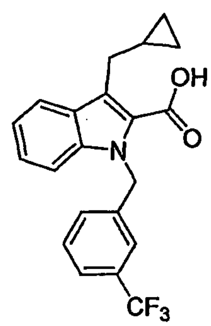


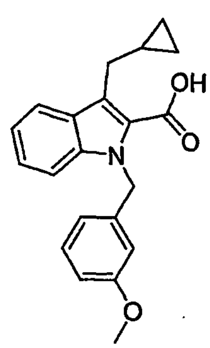


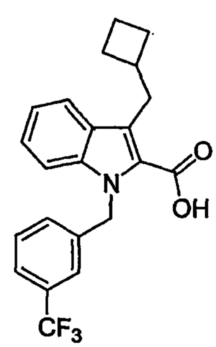


In another embodiment of the invention, R^3 is R^{12}-R^{13}, where R^{13} is cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl. Examples of compounds of the invention where R^3 is R^{12}-R^{13} include, but are not limited to:

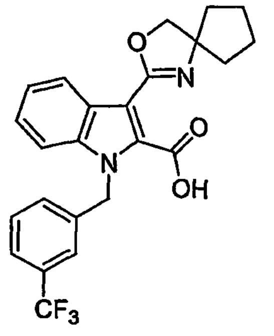


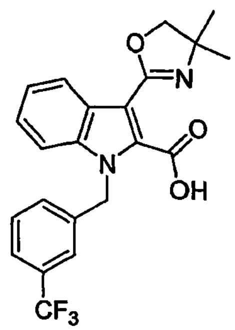




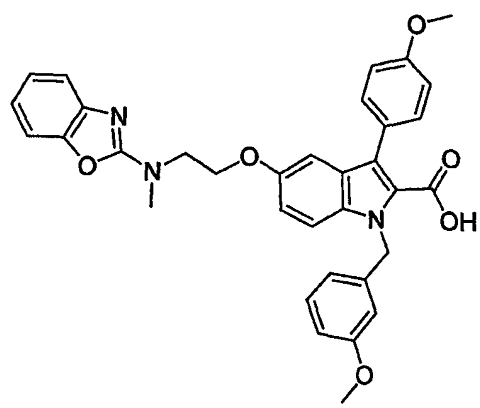


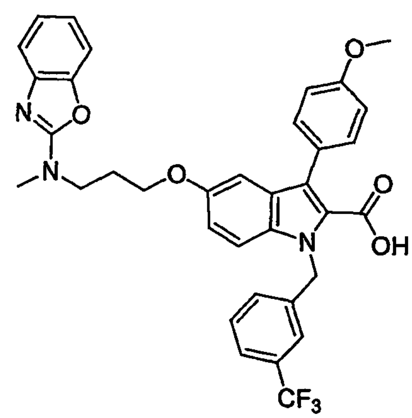
In other embodiments of the invention, R^3 is a cycloalkyl, heterocylcoalkyl, cycloalkenyl or heterocycloalkenyl, which may be substituted or may be fused with a spiro ring of 3-9 carbon atoms. Examples of compounds of the invention where R^3 is a cycloalkyl, heterocylcoalkyl, cycloalkenyl or heterocycloalkenyl include, but are not limited to:

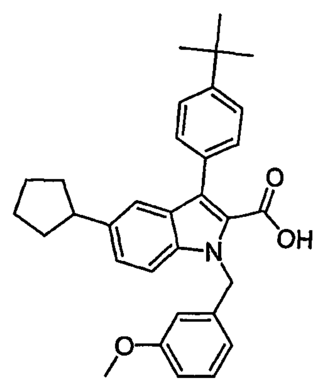


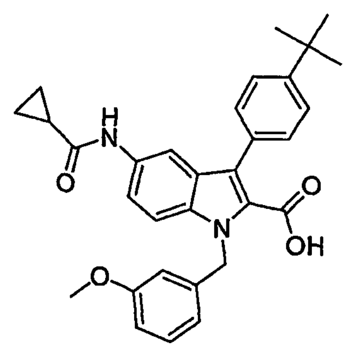


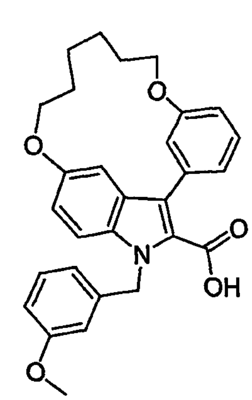
In still other embodiments of the invention, R^4, R^5, R^6 and/or R^7 may be other than hydrogen. Examples of compounds of the invention where R^4, R^5, R^6 and/or R^7 are other than hydrogen include, but are not limited to:

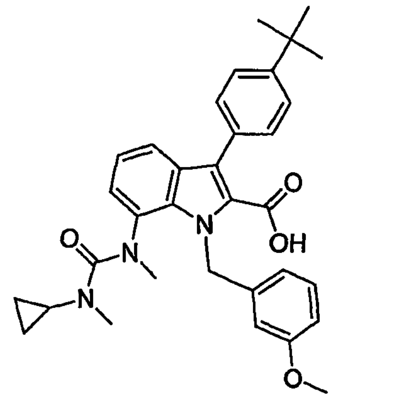


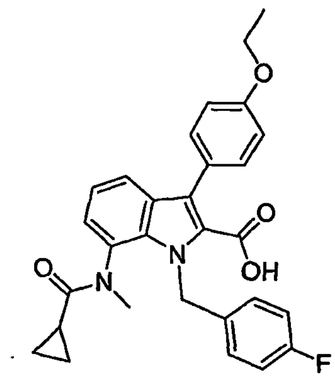


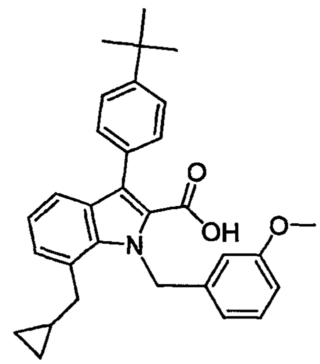


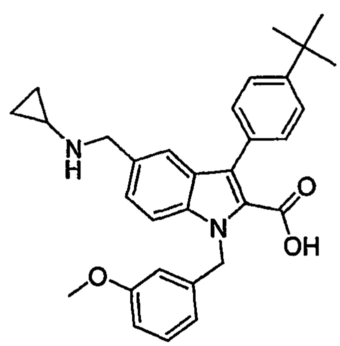


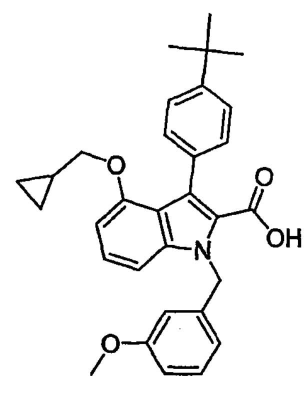


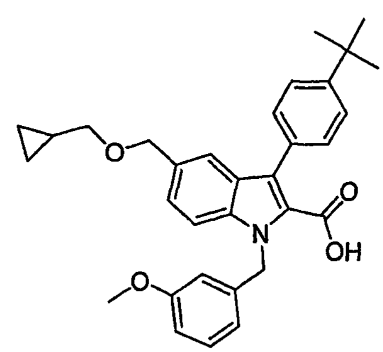


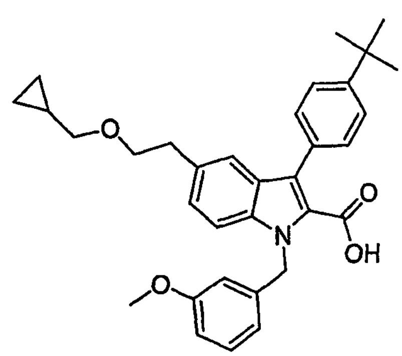


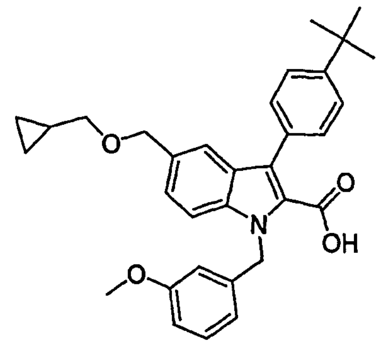


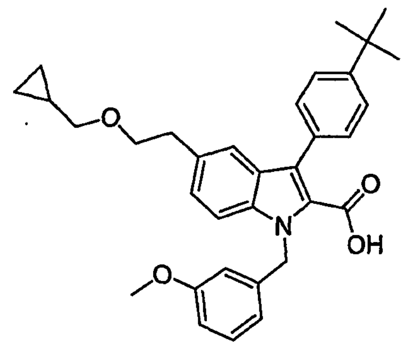


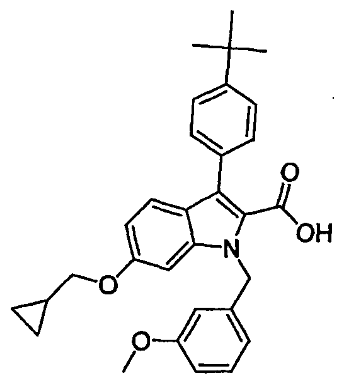


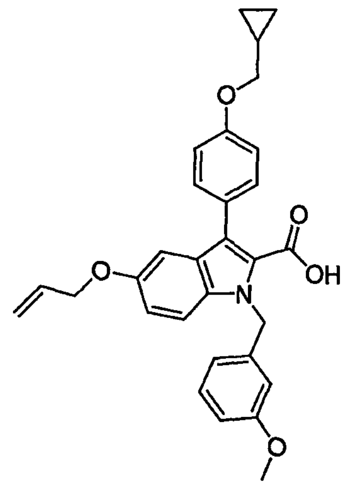


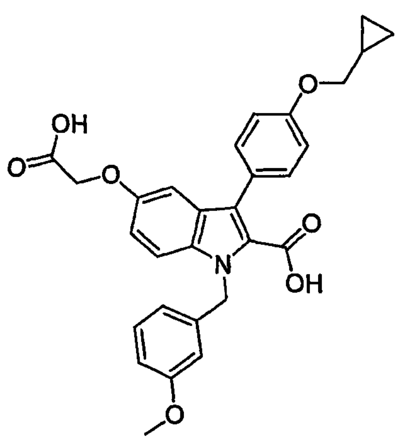


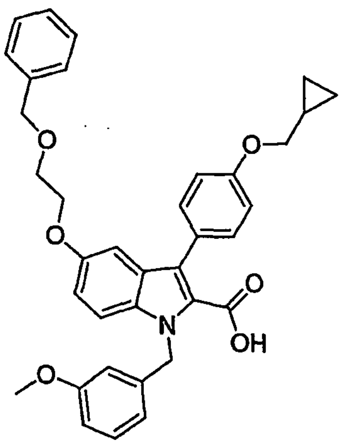

O
O
OH
N
O

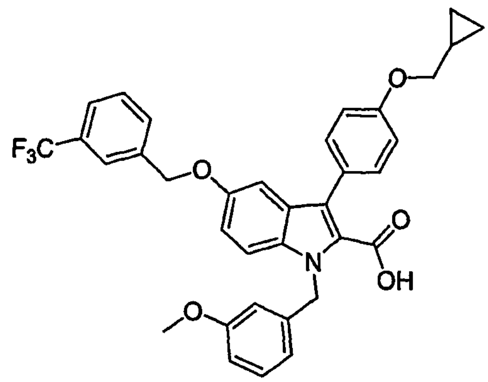
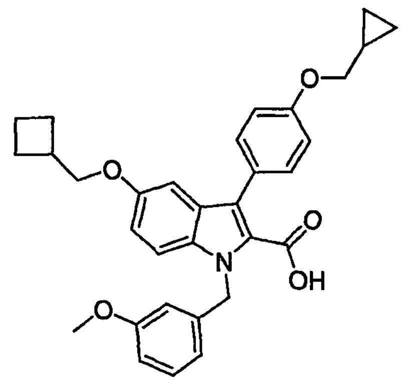

O
O
N
OH
O


O
OH
N
O
O


O
O
O
OH
N
O


O
OH
O
O
O
N
OH
O


O
O
O
O
N
OH
O

Compounds of Formulas I and IIa may be useful in the treatment or prevention of PPAR-γ mediated diseases or conditions. An agent which binds to PPAR-γ may be employed for a wide variety of indications, including, but not limited to:

(1) osteoporosis and osteopenia, *see,* Nuttall, *et al.*, Bone 27 (2), (2000), 177-184; Gimble, *et al.*, Bone 19 (5), (1996), 421-428;

(2) cancer, particularly PPAR-γ mediated cancers, such as breast and prostate cancers (*see,* Gelman, *et al.*, Cell. and Mol. Life Sci., 55 (6-7), (1999), 935-943; Kersten, *et al.*, Nature, 405 (6785), May 25, 2000, 421-424), colon cancer (*see*, Saez, *et al.*, Nat. Med., 4 (9) Sept. 1998, 1058-1061; Lefebvre, *et al.*, Nat. Med., 4 (9), Sept. 1998, 1053-1057; Demetri, *et al.*, Proc. Nat'l. Acad. Sci. USA, 96 (7), Mar. 30, 1999, 3951-3956) liposarcoma (Demetri, et al., Proc. Nat'l. Acad. Sci USA, 96 (7), Mar. 30, 1999, 3951-3956) and lung cancer (*see*, Chang, *et al.*, Cancer Res., 60, 2000, 1129-1138);

(3) hyperglycemia, type 1 diabetes, type 2 diabetes, syndrome X, and insulin resistance, (*see* Lehmann, *et al.*, J. Bio. Chem., 270 (22) (1995), 12953-12956; Spiegelman, Diabetes, 47 (4), (1998), 507-514);

(4) obesity, (*see* Zhou, *et al.*, Proc. Nat'l. Ac. Sci. USA, 96 (5), (1999), 2391-2395; U.S. Patent No. 6,033,656);

(5) inflammation, particularly inflammatory bowel disease (*see* Cell. and Mol. Life Sci., 55 (6-7), (1999), 935-943), Alzheimer's disease (*see*, Combs, *et al*, J. Neurosci. 20 (2), 2000, 558-567), rheumatoid arthritis (*see*, Jiang, *et al.*, Nature 391 (6662), 1998, 82-86), and atherosclerosis (*see* Pasceri, *et al.*, Circulation, 101 (3), 2000, 235-238);

(6) cardiovascular disease, particularly hypertension, (*see* Cell. and Mol. Life Sci., 55 (6-7), (1999), 935-943 review);

(7) dyslipidemia, hypertriglyceridemia, diabetic dyslipidemia, hyperlipidemia and hypercholesteremia (*see* Hulin, *et al.*, Curr. Pharm. Design, 2 (1996), 85-102); and

(8) skin disorders, particularly inflammatory skin disorders caused by lupus erythematosus, and acne, psoriasis, dermatitis, eczema and keratosis (*see*, WO 99/34783; U.S. Patent No. 5,981,586).

Compounds of Formulas I and IIa are preferably used in the treatment or prevention of osteopenia, osteoporosis, and PPAR-γ mediated cancers, including breast, prostate and colon cancer.

The present invention also includes pharmaceutically acceptable salts of the compounds of Formulas I and IIa. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (*e.g.*, Li^+ Na^+ or K^+), alkaline earth cations (*e.g.*, Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary

ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

A number of the compounds of Formulas I and IIa possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to the skilled in the art. The present invention encompasses any racemic or optically active forms of compounds described in Formula I or Formula IIa which possess PPAR-γ modulating activity or the use of any racemic or optically active forms of the compounds described in Formulas I and IIa for the treatment or prevention of PPAR-γ mediated diseases or conditions.

The therapeutic agents of the invention may be employed alone or concurrently with other therapies. For example, when employed as a treatment for osteoporosis or osteopenia, the compounds of the invention may be used in combination with a calcium source, vitamin D or analogues of vitamin D, and/or antiresorptive therapies such as estrogen replacement therapy, treatment with a fluoride source, treatment with calcitonin or a calcitonin analogue, or treatment with a bisphosphonate such as alendronate. The method of the invention is intended to be employed for treatment of PPAR-γ mediated diseases or conditions in both humans and other mammals.

The compounds may be administered orally, dermally, parenterally, by injection, by inhalation or spray, or sublingually, rectally or vaginally in dosage unit formulations. The term "administered by injection" includes intravenous, intraarticular, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and, if desired, other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already

mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, *e.g.*, oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal or vaginal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of the invention may also be administered transdermally using methods known to those skilled in the art (*see, e.g.*, Chien; "Transdermal Controlled Systemic Medications"; Marcel Dekker, Inc.; 1987. Lipp *et al.* WO 94/04157 3Mar94). For example, a solution or suspension of a compound of Formula I or IIa in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with

additional additives known to those skilled in the art, such as matrix materials and bacteriocides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of Formula I or IIa may be formulated into a lotion or salve.

Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery systems are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C_8-C_{18} fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated C_8-C_{18} fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl isobutyl *tert*-butyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbid and diethyleneglycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated C_8-C_{18} fatty alcohols, saturated or unsaturated C_8-C_{18} fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers,

styrene-butadiene coploymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

For all regimens of use disclosed herein for compounds of Formulas I and IIa, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, *i.e.*, the mode of treatment and the daily number of doses of a compound of Formula I or IIa or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

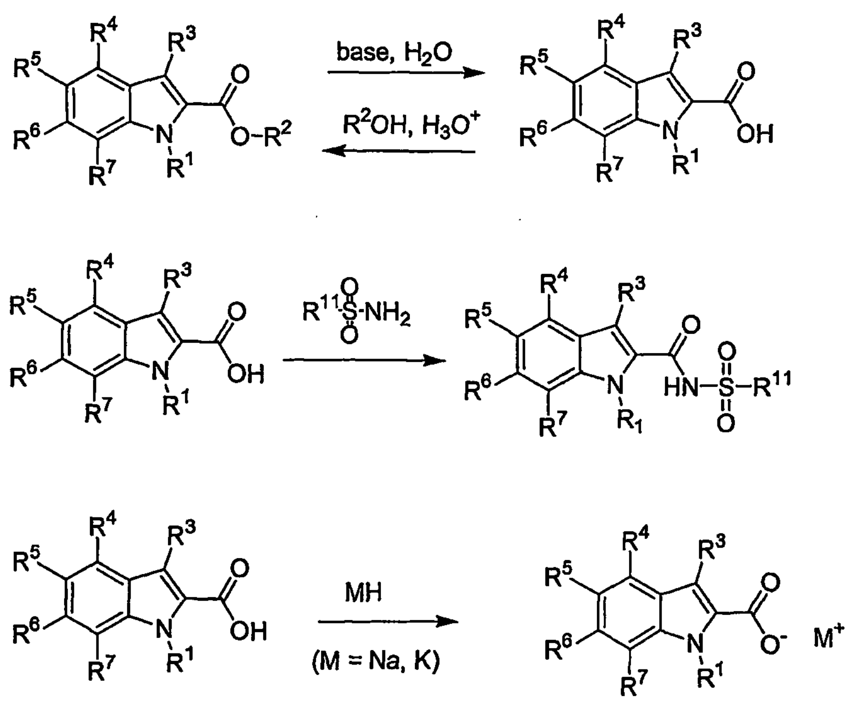
The compounds of Formulas I and IIa may be prepared by use of known chemical reactions and procedures, from known compounds (or from starting materials which, in turn, are producible from known compounds) through the preparative methods shown below, as well as by other reactions and procedures known to the skilled in the art. Such reactions and procedures include, but are not limited to, esterification, hydrolysis, alkylation, acylation neutralization, coupling, oxidation, reduction, condensation,

elimination and substitution reactions. Nevertheless, the following general preparative methods are presented to aid practitioners in synthesizing the compounds of the invention, with more detailed particular examples being presented in the experimental section. The examples are for illustrative purposes only and are not intended, nor should they be construed, to limit the invention in any way.

Within the scope of each method, optional substituents may appear on reagents or intermediates which may act as protecting groups or other non-participating groups. Utilizing methods well known to those skilled in the art, such groups are introduced and/or removed during the course of the synthetic schemes to provide the compounds of the present invention. All variable groups not defined below are as described hereinabove.

In general, compounds of Formula I or IIa may be prepared from the appropriately substituted indoles, by esterification, hydrolysis, sulfonylation or neutralization reactions as shown in Flow Diagram I:

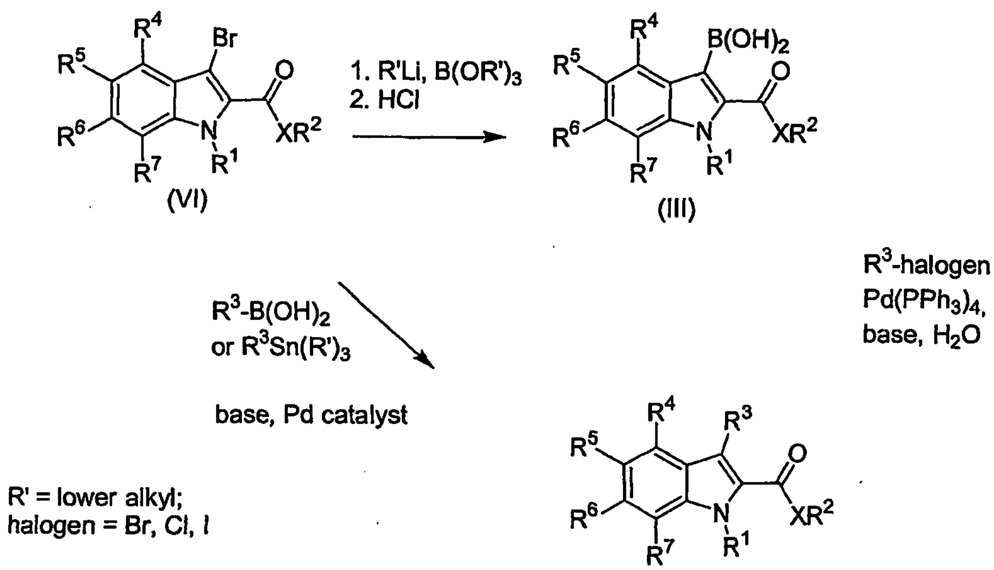
Flow Diagram I



Preparation of certain Formula I compounds with a variety of R^3 substituents may be prepared by a sequence involving conversion of VI to a boronic acid intermediate,

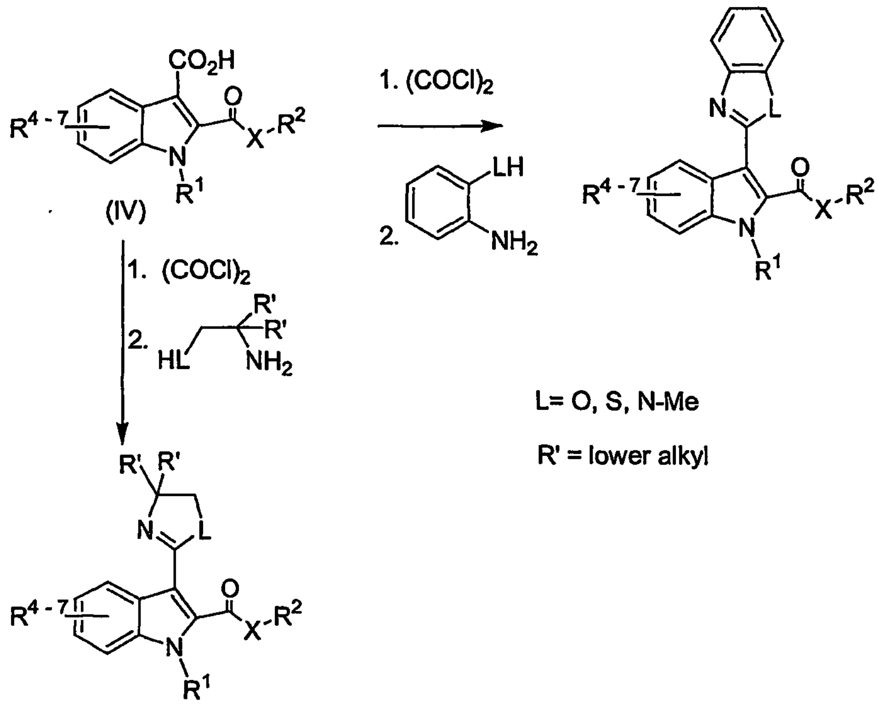
followed by a palladium-facilitated coupling reaction with an organohalide and base, such as triethylamine, potassium carbonate or Huenig's base, as shown in Flow Diagram II. Alternatively, either a boronic acid or organotin intermediate may be coupled with VI under similar conditions.

Flow Diagram II



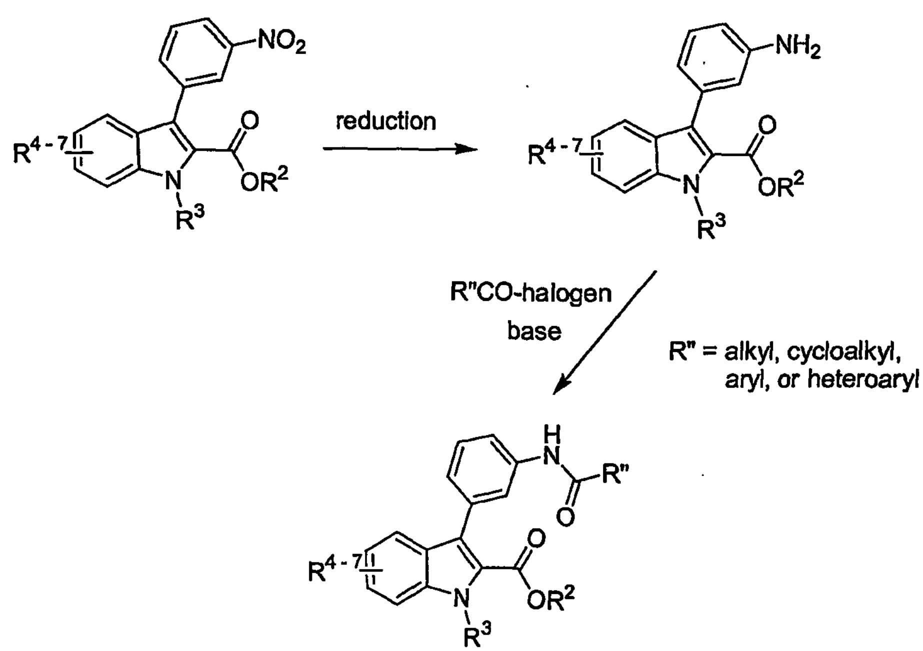
Other compounds with heterocycloakenyl or heteroaryl substituents at the R^3 position may prepared by condensation of 3-carboxy-substituted indoles with 2-aminoethanols, 2-aminophenols or 2-aminothiols as illustrated in Flow Diagram III.

Flow Diagram III



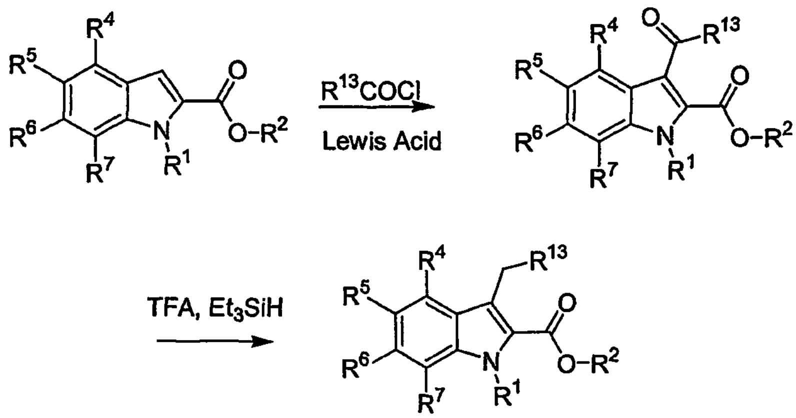
Certain aryl substituents on the R^3 aryl ring may be further transformed to other substituents by standard means. An illustration of this is shown in Flow Diagram IV, in which a nitro group is reduced and acylated to provide amido substituents.

Flow Diagram IV



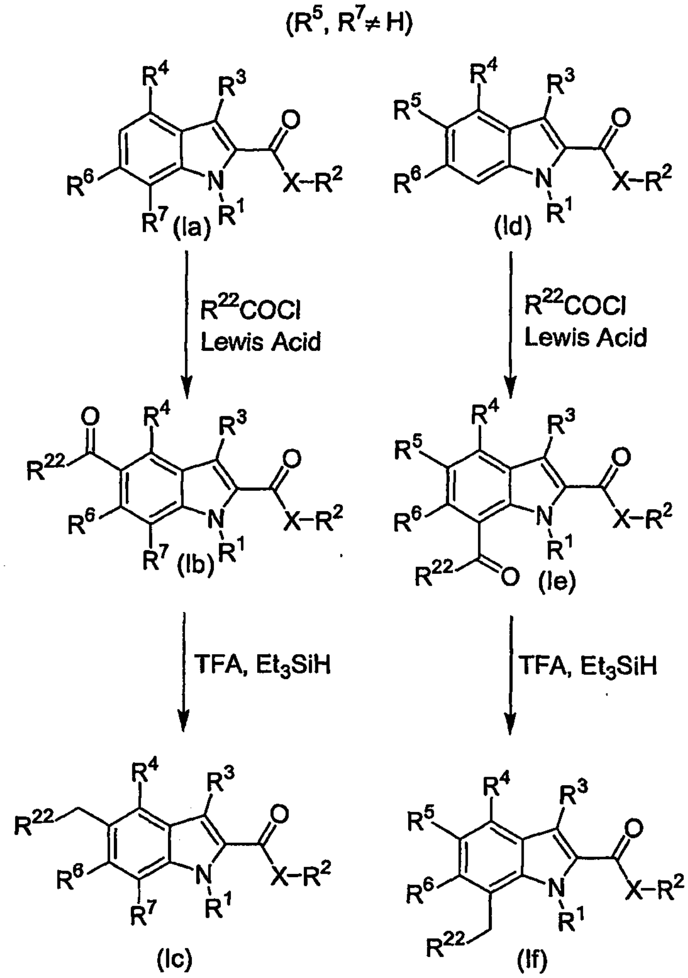
Compounds of Formula I which bear certain R^3 substituents may be prepared by Friedel-Crafts acylation of the corresponding unsubstituted indole, followed by reduction of the carbonyl group to a methylene, as shown in Flow Diagram V.

Flow Diagram V

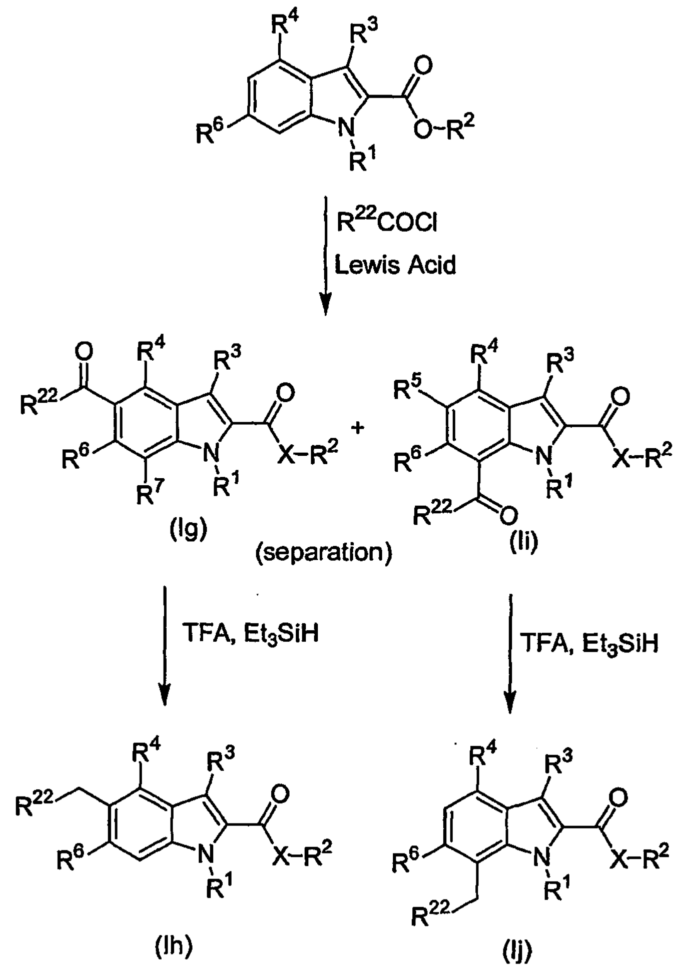


Compounds of Formula I with similar substituents at either R^5 or R^7 may be likewise prepared, either individually (Flow Diagram VI) or as mixtures (Flow Diagram VII) by an analogous sequence of acylation and reduction reactions. In the latter scheme, where R^5 and R^7 are hydrogen in the starting materials, individual compounds may be obtained by chromatographic separation of products (Ig and Ii) after the initial step.

Flow Diagram VI

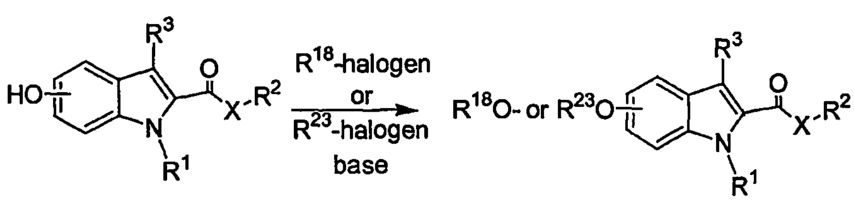

(R5, R7≠ H)
(Ia)
(Id)
R22COCl
Lewis Acid
(Ib)
(Ie)
TFA, Et3SiH
(Ic)
(If)

Flow Diagram VII



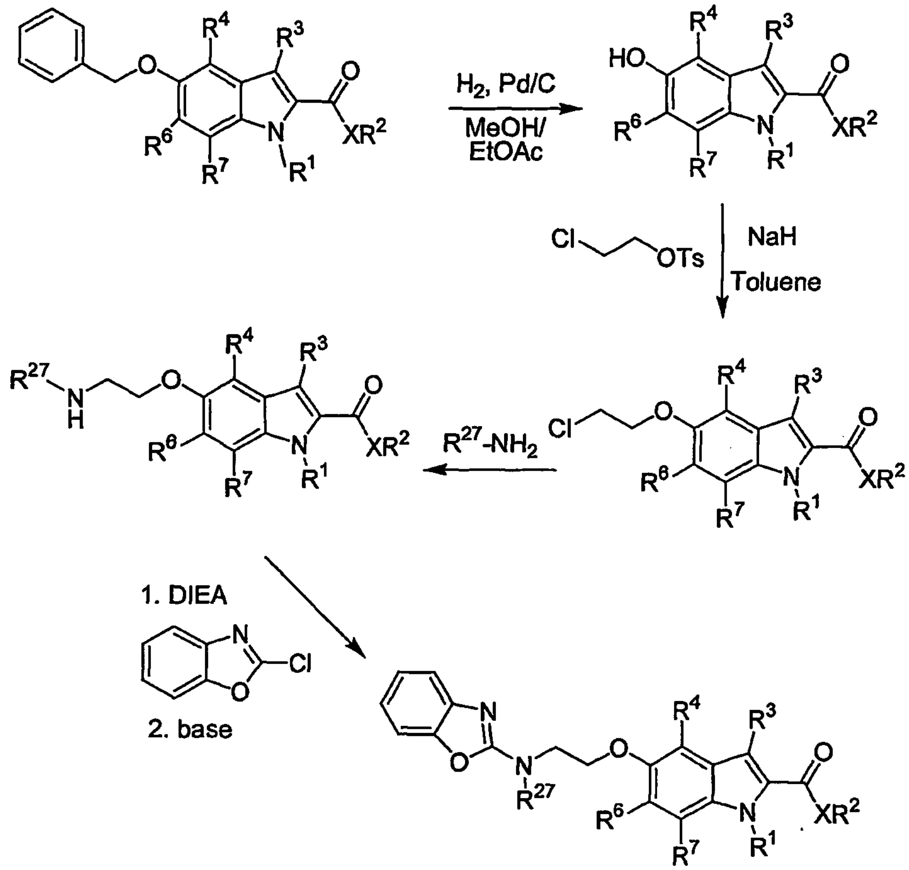
O-Alkylation reactions may be utilized to prepare Formula I compounds bearing substituents on R^4, R^5, R^6 or R^7 positions. For example, alkylation of the corresponding hydroxy intermediates provides ethers containing an R^{18} or R^{23} group, depending upon position, as shown in Flow Diagram VIII.

Flow Diagram VIII



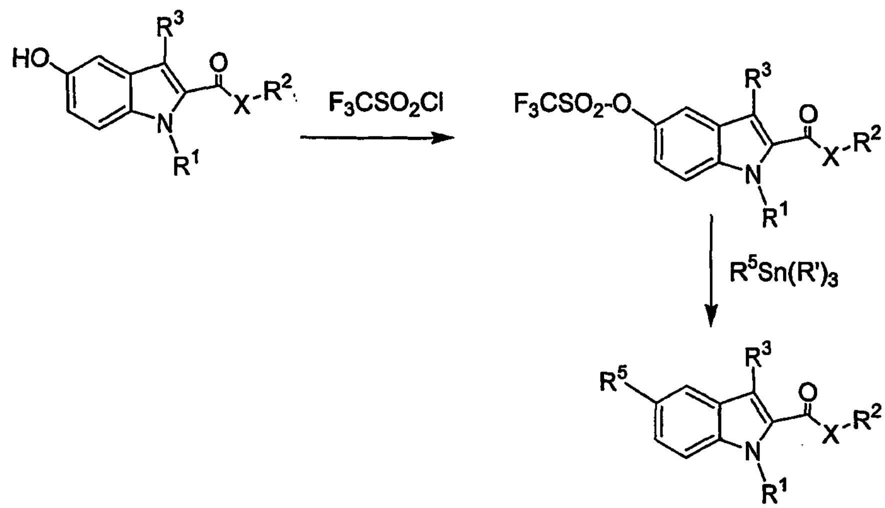
A more detailed example of this process is shown for compounds bearing R^5 the group in Flow Diagram IX.

Flow Diagram IX



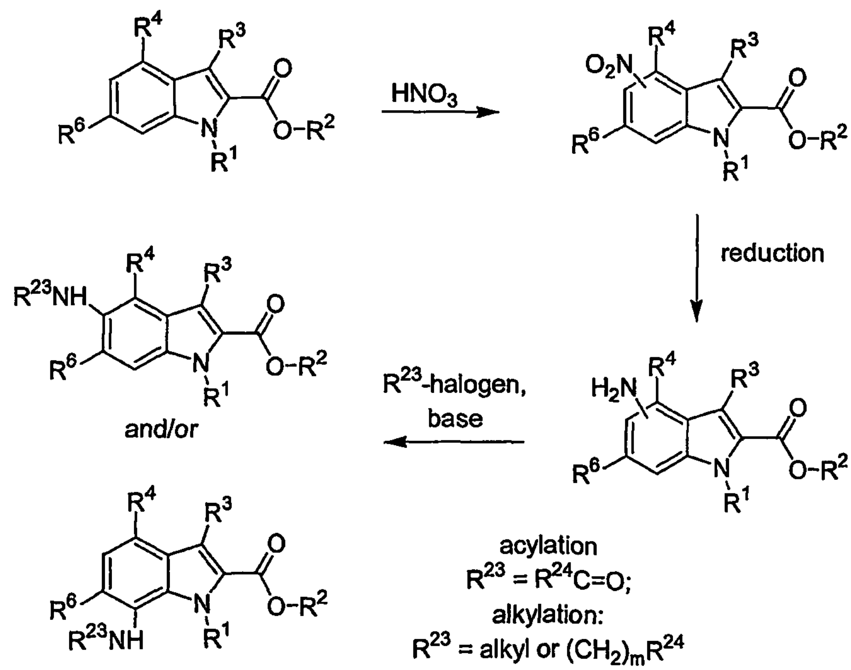
Other compounds of Formula I may also be obtained from a hydroxy intermediate. For example, the hydroxy group may be converted to a trifluoromethylsulfonate which reacts with an alkyl stannane to give alkyl-substituted indoles, as exemplified in Flow Diagram X for the R^5 position.

Flow Diagram X



Nitration of indoles that are unsubstituted at positions 5 and/or 7 provides nitro-substituted intermediates which may be reduced and either acylated or alkylated to give a variety of Formula I compounds as shown in Flow Diagram XI.

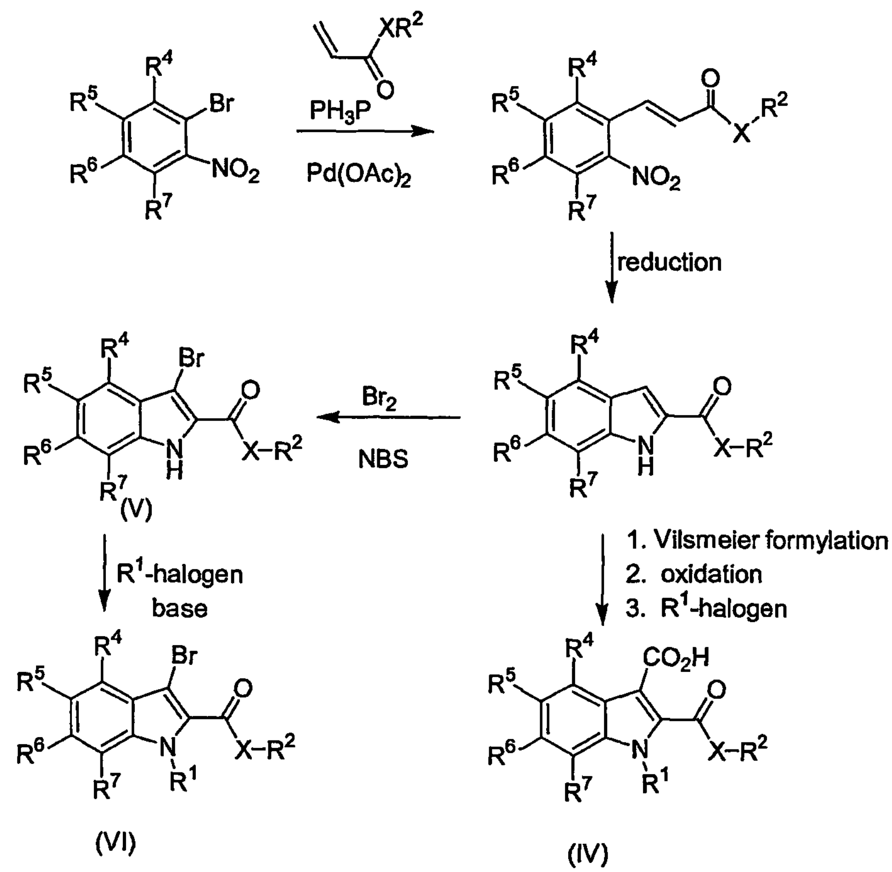
Flow Diagram XI



Indole intermediates which are useful in the preparation of compounds in the present invention are either commercially available or may be prepared by standard methods. These transformations are summarized in Flow Diagram XII for intermediates

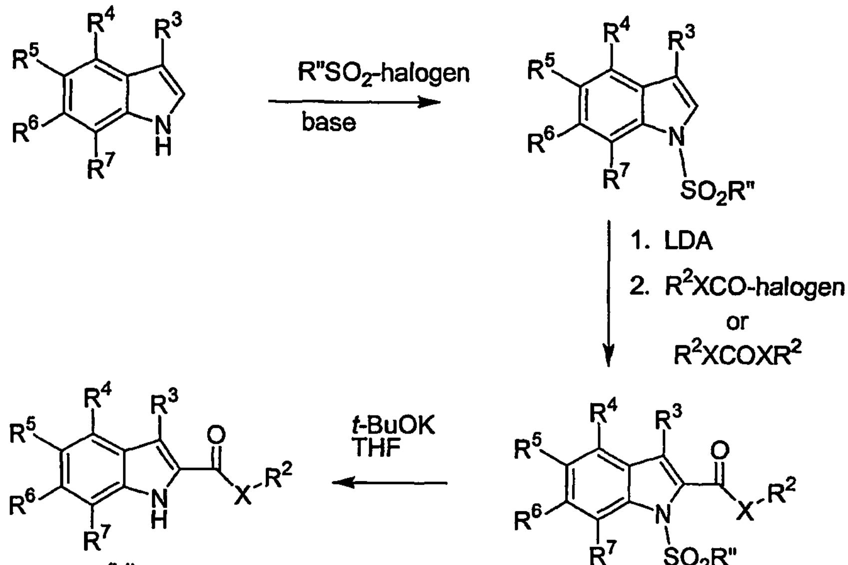
of Formula VI, IV and V. For example, an appropriately substituted 2-bromonitrobenzene may be converted to a 2-nitrocinnamic acid derivative which cyclizes to an indole upon reduction. The resulting indole intermediate may then be brominated at the 3 position, and the desired R^1 substituent introduced by N-alkylation giving the intermediate compounds of Formula VI. Compounds of Formula IV may be prepared from VI in a stepwise sequence involving halogen-metal exchange, addition to formaldehyde, and oxidation of the resulting carbinol to a 3-carboxylic acid. It is understood that the presence of certain R^4-R^7 substituents may require additional steps of protection and deprotection during this process in order to avoid undesired side reactions.

Flow Diagram XII



The introduction of the carboxyl functionality at position 2 of other indole compounds may be accomplished by a sequence shown in Flow Diagram XIII. The nitrogen of the unsubstituted indole is first protected as a sulfonamide, then subjected to acylation conditions catalyzed by Lewis acid. Protection may be then be removed and the desired R^1 attached as described above.

Flow Diagram XIII



(V)

Preparative Examples

Examples of preparations of both intermediates and compounds of the invention are provided in the following detailed synthetic procedures. In the tables of compounds to follow, the synthesis of each compound is referenced back to these exemplary preparative steps. All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by volume.

All reactions were performed under a positive pressure of dry argon, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. Thin-layer chromatography (TLC) was performed on Whatman® pre-coated, glass-backed silica gel 60A F-254 250 μm plates. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel. Melting points (mp) were determined using a Thomas-Hoover melting point apparatus, an Electrothermal melting point apparatus, or a Mettler FP66 automated melting point apparatus and are uncorrected.

^{1}H-NMR spectra were recorded with a Varian Mercury (300 MHz,) or a Bruker Avance 500 (500 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated

solvent ($CDCl_3$ δ 7.26; CD_3OD δ 3.30; DMSO-D_6 δ 2.49; Acetone-D_6 δ 2.04; or CD_3CN δ 1.94).

HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a YMC Pro C18 2.0 mm x 23 mm column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Gradient elution from 90% A to 95% B over 4 minutes was used on the HPLC. Buffer A was 98% water, 2% Acetonitrile and 0.02% TFA. Buffer B was 98% Acetonitrile, 2% water and 0.018% TFA. Spectra were scanned from 140-1200 amu using a variable ion time according to the number of ions in the source.

Fourier transform infrared spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer.

Elemental analyses were conducted by Robertson Microlit Labs, Madison NJ. NMR mass and infrared spectra, and elemental analyses of the compounds were consistent with the assigned structures.

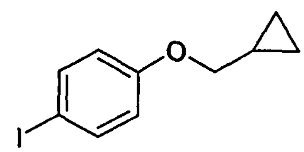
List of Abbreviations and Acronyms

As employed herein, the following terms have the indicated meanings.

Ac_2O	acetic anhydride
AIBN	2,2'-azobisisobutyronitrile
anh	anhydrous
aq	aqueous
BOC	*tert*-butoxycarbonyl
BuLi	*n*-butyllithium
calc'd	calculated
Celite®	diatomaceous earth
conc.	concentrated
mCPBA	3-chloroperoxybenzoic acid
dec.	decomposition
DAST	(diethylamino)sulfur trifluoride
DIAD	diisopropyl azodicarboxylate

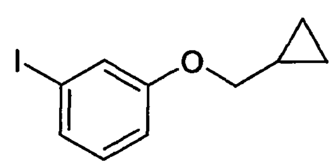
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
DPPF	bis(diphenylphosphino)ferrocene
EDCI·HCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Et_3N	triethylamine
$KN(SiMe_3)_2$	potassium bis(trimethylsilyl)amide
KO*t*Bu	potassium *tert*-butoxide
$LiAlH_4$	lithium aluminum hydride
$LiBH_4$	lithium borohydride
$LiN(SiMe_3)_2$	lithium bis(trimethylsilyl)amide
MeOH	methanol
NMM	4-methylmorpholine
obs'd	observed
Oxone®	potassium peroxymonosulfate
PCC	pyridinium chlorochromate
Ph_3P	triphenylphosphine
$PdCl_2(dppf)$	[1,1'-bis(diphenylphosphino)ferrocene]dichloro paladium(II)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PivCl	trimethylacetyl chloride
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDMSOTf	*tert*-butyldimethylsilyl triflate
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TRIBAL	triisobutylaluminum

Example 1
4-(Cyclopropylmethoxy)iodobenzene



A solution of 4-iodophenol (11.0g, 50.0 mmol) in tetrahydrofuran (30 mL + 10 mL rinse) was added to a cooled (0 °C) and stirred suspension of sodium hydride (1.44 g, 60.0 mmol) in tetrahydrofuran (30 mL). The cold bath was removed and the reaction was stirred for 1 h. A solution of (bromomethyl)cyclopropane (16.2 g, 120.0 mmol) in tetrahydrofuran (20 mL) and then HMPA (5 mL) were added successively and the reaction was heated (55 °C) for 18 h. After cooling, the reaction was quenched with cold water (500 mL) and then extracted with ethyl acetate (3x200 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 10% dichloromethane/hexane afforded 12.6 g (92%) of the desired Example 1. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 2 H), 6.68 (d, 2 H), 3.76 (d, 2 H), 1.20-1.35 (m, 1 H), 0.60-0.70 (m, 2 H), 0.31-0.39 (m, 2 H); mass spectroscopy gave M^+ of 274.0 (calc'd exact mass for $C_{10}H_{11}IO$ = 273.99).

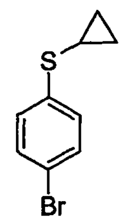
Example 2
3-(Cyclopropylmethoxy)iodobenzene



3-Iodophenol (11.0g, 50.0 mmol) was converted to 12.4 g (90%) of the desired product using the method described for Example 1. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.31 (m, 2 H), 6.99 (dd, 1 H), 6.84-6.90 (m, 1 H), 3.77 (d, 2 H), 1.25-1.35 (m, 1 H), 0.60-0.70 (m, 2 H), 0.32-0.39 (m, 2 H); mass spectroscopy gave MH^+ of 275.0 (calc'd exact mass for $C_{10}H_{11}IO$ = 273.99).

Example 3

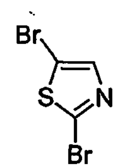
4-Bromo-1-cyclopropylthiobenezene



To a solution of cyclopropylphenyl sulfide (5 g, 34.2 mmol) in 342 mL chloroform, a solution of bromine (1.94 g, 37.6 mmol) in 113 mL chloroform was added dropwise. The reaction mixture was stirred at rt overnight and then quenched with aq. $NaHCO_3$ and sat. $Na_2S_2O_5$. The reaction was extracted with dichloromethane and the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. An oil (6.19 g, 79% yield) was given after distillation. ^{1}H NMR (DMSO, δ = 2.48): 7.45 – 7.49 (m, 2H), 7.25 – 7.30 (m, 2H), 2.22 – 2.28 (m, 1H), 1.04 – 1.10 (m, 2H), and 0.53 - 0.58 (m, 2H). MS [M+H] = 229 (HPLC/MS).

Example 4

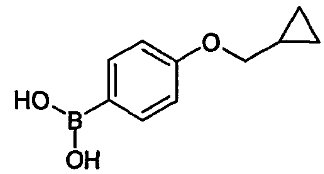
2,5-Dibromo-1,3-thiozole



(Caution: Blast shield recommended). Nitric acid (65%, 11.6 mL) was added slowly to a 0°C solution of commercially available 2-amino-5-bromothiazole monohydrobromide (10 g, 38.4 mmol) in phosphoric acid (85%, 30 mL). The mixture was cooled to –5°C and an aq. solution of sodium nitrite (3.44 g, 50 mmol) was added slowly, while maintaining the bath temperature below 0°C. The mixture was stirred for 2 h. A solution of copper sulfate (8.0 gm) and sodium bromide (10.3 g) in water (30 mL) was added slowly at 0°C and the resulting mixture was stirred for 4 h. The mixture was adjusted to pH 7 and extracted with ether. The combined extracts were dried and concentrated under reduced pressure. Purification of the remaining oil by flash chromatography (silica gel, 10:1 hexane:ethyl acetate) afforded 4.3 g (46%) of Example 4. Rf = 0.91 (10/1 hexane/ethyl acetate); GCMS (CI) obs'd: 242, 244, 246; calc'd 241.

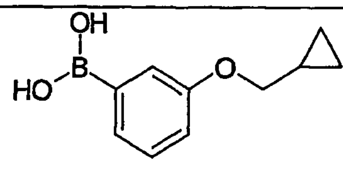
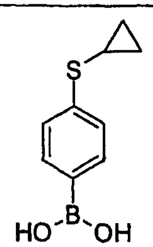
Example 5

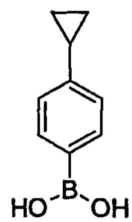
4-(Cyclopropylmethoxy)phenylboronic acid



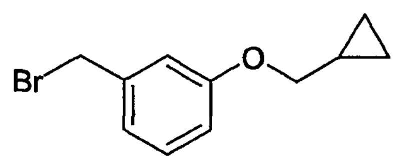
Butyl lithium (2.5 M in hexane, 14.4 mL, 36 mmol) was added dropwise (5 min) to a cooled (-78 °C) and stirred solution of 4-(cyclopropylmethoxy)iodobenzene **1** (9.00 g, 32.8 mmol) in tetrahydrofuran (100 mL). After 20 min, trimethyl borate (11.3 mL, 10.4 g, 100 mmol) was added dropwise (10 mL). The reaction was stirred for an additional 20 min, and was then allowed to warm to rt. The reaction was quenched with 1 M hydrochloric acid (300 mL) and stirring was continued for 30 min. The product was extracted with diethyl ether (4x100 mL) and then the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in toluene and then concentrated. This operation was repeated (5x) until the distillate was colorless and left 5.67 g (90%) of crude product. This material was used without purification or analysis.

The following compounds were prepared according to the method of Example **5**:

Ex. No.	**Structure**	**Yield [%]**	**MS [M+H⁺]**	**Rf**	**mp [°C]**
6		93			
7		75			

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
8		85			

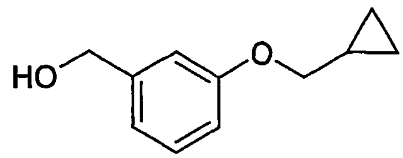
Example 9
1-(Bromomethyl)-3-(cyclopropylmethoxy)benzene



Pyridine (3.20 mL, 3.13 g, 39.6 mmol) and a solution of dibromophenylphosphorane (13.9 g, 32.9 mmol) in acetonitrile (50 mL) were added successively to a cooled (0 °C) and stirred solution of 1-(hydroxymethyl)-3-(cyclopropylmethoxy)benzene, (Example **10**, 4.40 g, 24.7 mmol) in acetonitrile (100 mL). The mixture was allowed to warm to rt and stirring was continued for 16 h. The reaction was quenched with saturated aqueous sodium thiosulfate (300 mL) and extracted with ethyl acetate (3x200 mL). The combined organic extracts were washed with 1 M hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 20% ethyl acetate/hexane gave 3.80 g (64%) of the Example **9**. The product had: ^{1}H NMR (300 MHz, acetone-D_6) d 7.22 (t, 1 H), 7.01 (m, 2 H), 6.82-6.88 (m, 1 H), 4.56 (s, 2 H), 3.83 (d, 2 H), 1.16-1.29 (m, 1 H), 0.52-0.62 (m, 2 H), 0.31-0.41 (m, 2 H).

Example 10

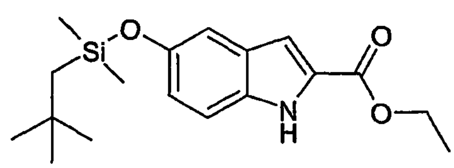
1-(Hydroxymethyl)-3-(cyclopropylmethoxy)benzene



Sodium borohydride (0.75 g, 20 mmol) was added in portions to a stirred solution of 3-(cyclopropylmethoxy)benzaldehyde (Lit: *Chem. Pharm. Bull.* **1975**, *23*, 2878) (3.5g, 20 mmol) in methanol (80 mL). The mixture was stirred for 2 h and then quenched with water (300 mL). The product was extracted with ethyl acetate (3x150 mL) and then the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to leave 3.2 g (89%) of crude product. This material was used in the next reaction without further purification or analysis.

Example 11

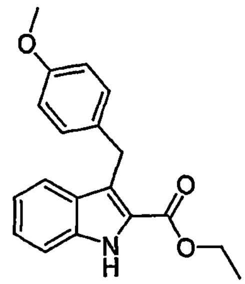
Ethyl 5-(*tert*-butyldimethylsiloxy)-1H-indole-2-carboxylate



Imidazole (2.30 g, 33.2 mmol) and *tert*-butyldimethylsilyl chloride (2.50 g, 16.6 mmol) were added successively to a stirred solution of ethyl 5-hydroxy-1H-indole-2-carboxylate (1.70 g, 8.29 mmol) in dichloromethane (100 mL). The reaction was stirred for 16 h and then diluted with dichloromethane (300 mL). The solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to leave 2.65 g (100%) of Example **11**. The product had: ^{1}H NMR (300 MHz, acetone-D_6) d 10.73-10.88 (br s, 1 H), 7.39 (d, 1 H), 7.11 (d, 1 H), 7.05 (s, 1 H), 6.86 (dd, 1 H), 4.34 (q, 2 H), 1.36 (t, 3 H), 1.09 (s, 9 H), 0.20 (s, 6 H).

Example 12

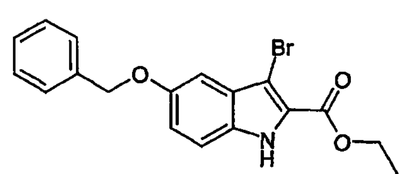
Ethyl 3-[(4-methoxyphenyl)methyl]indole-2-carboxylate



To a solution of ethyl 1-[(4-methoxyphenyl)methyl]indole-2-carboxylate (Example **38**) (950 mg, 3.07 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (1.2 mL). The resulting pink solution was stirred for 18 h at RT. The reaction was quenched with 1.0 N aqueous sodium hydroxide and the organic layer was collected. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous magnesium sulfate, concentrated to an oil, and purified by flash chromatography on silica in 8:1 hexane: ethyl acetate (v/v) to yield 468 mg (49%) of Example **12** of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (s, 1H), 7.64-7.58 (m, 1H), 7.42-7.38 (m, 1H), 7.26-7.14 (m, 3H), 7.02-6.97 (m, 1H), 6.80-6.74 (m, 2H), 4.35 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 3.65 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); TLF R_f = 0.44 (4:1 Hexane: ethyl acetate (v/v)).

Example 13

Ethyl 5-(benzyloxy)-3-bromo-1H-indole-2-carboxylate

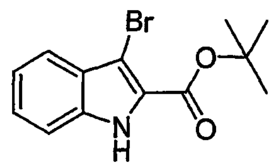


A solution of *N*-bromosuccinimide (7.83 g, 44.0 mmol) in *N,N*-dimethylformamide (30 mL) was added dropwise (40 min) to a cooled (0 °C) and stirred solution of ethyl 5-(benzyloxy)-1H-indole-2-carboxylate (10.0 g, 39.2 mmol) in *N,N*-dimethylformamide (20 mL). The cold bath was removed and stirring was continued for an additional 1.5 h. The reaction was poured over ice water (600 mL) and the resulting precipitate was collected by vacuum filtration. The precipitate was washed with water and

dried to give 12.9 g (98%) of crude product. This material was used in the next reaction without further purification or analysis.

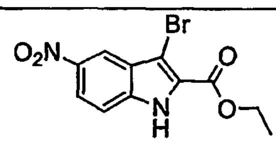
Example 14

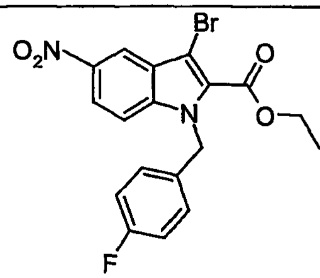
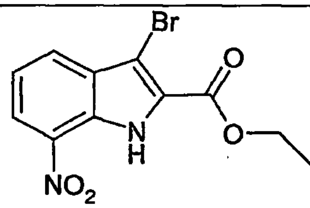
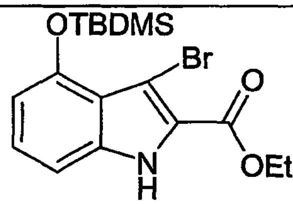
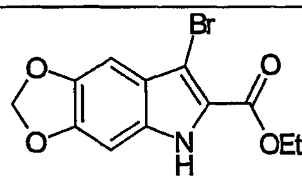
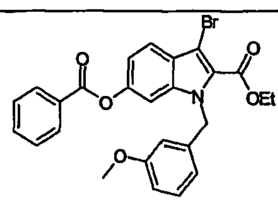
tert-Butyl 3-Bromoindole-2-carboxylate

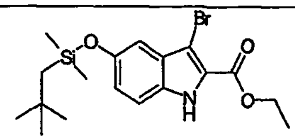


Indole-2-carboxylic acid was converted to 3-bromoindole-2-carboxylic acid using the method described for Example **13**. *N,N*-dimethylformamide di-*tert*-butyl acetal (35 mL) was added dropwise to a stirring mixture of indole-3-bromo-2-carboxylic acid (14.9 g, 62 mmol) suspended in toluene (100 mL). After the addition was complete, the reaction was heated at 90 °C for 8 h. The reaction mixture was then cooled to room temperature and washed with cold water (2x100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield the crude *tert*-butyl 3-bromoindole-2-carboxylate, assume quantitative yield. The crude product was used in the next step without purification.

The following compounds were prepared according to the methods of Examples **13** and **14**:

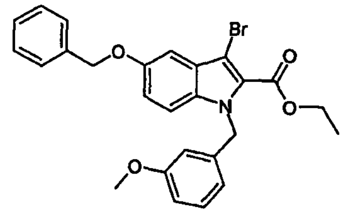
Ex. No.	Structure	Yield [%]	MS [M+H⁺]	Rf	mp [°C]
15		96		0.58 (Hexane /ethyl acetate 2:1)	

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
16		58		0.70 (Hexane /ethyl acetate 2:1)	
17		100	312.5		
18		73	398		
19		87		0.4 (Hexane /ethyl acetate 8:2)	
20		92	508.1	0.27 (Hexane /ethyl acetate 8:2)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
21		89			

Example 22

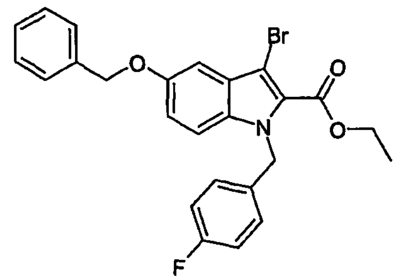
Ethyl 5-(benzyloxy)-3-bromo-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Powdered potassium carbonate (2.79 g, 20.2 mmol) and 3-methoxybenzyl bromide (2.03 g, 10.1 mmol) were added successively to a stirred solution of ethyl 5-(benzyloxy)-3-bromo-1H-indole-2-carboxylate, Lit. WO96/18393 (3.63 g, 9.70 mmol) in *N,N*-dimethylformamide (20 mL). The reaction was stirred for 23 h and then diluted with water (250 mL). The product was extracted with ethyl acetate (3x100 mL) and then the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Recrystalization of the residue using methanol afforded 4.03 g (84%) of the desired product. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05-7.91 (m, 9 H), 6.74 (dd, 1 H), 6.53-6.63 (m, 2 H), 5.37 (s, 2 H), 5.12 (s, 2 H), 4.37 (q, 2 H), 3.71 (s, 3 H), 1.39 (t, 3 H); mass spectroscopy gave MH$^+$ = 494.1 (calc'd exact mass for $C_{26}H_{24}BrNO_4$ = 493.09).

Example 23

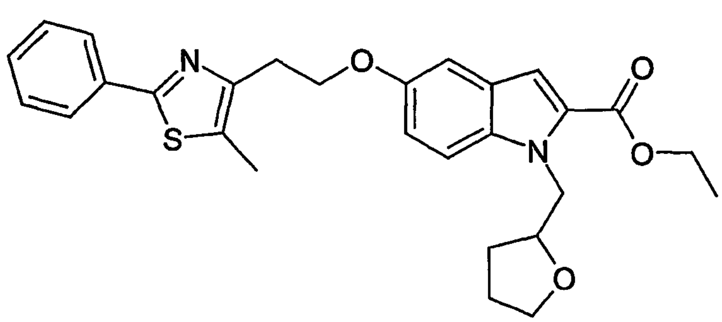
Ethyl 5-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)-1*H*-indole-2-carboxylate



A solution of ethyl 5-(benzyloxy)-3-bromo-1*H*-indole-2-carboxylate, Ref. WO96/18393 (6.77 g, 20.3 mmol, Ref. 96/18393) in *N,N*-dimethylformamide (10 + 5 mL rinse) was added slowly (10 min) to a cooled (0 °C) and stirred suspension of sodium hydride (0.72 g, 30 mmol) in *N,N*-dimethylformamide (30 mL). The reaction was stirred for 1 h and then 4-fluorobenzylbromide (3.7 mL, 5.7 g, 30 mmol) was added. The cold bath was removed and the mixture was stirred for 18 h. The reaction was quenched by pouring over ice water (400 mL) and then the product was extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 50% dichloromethane/hexane gave 6.80 g (75%) of the desired product containing trace impurities. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84-7.53 (m, 12 H), 5.72 (s, 2 H), 5.13 (s, 2 H), 4.38 (q, 2 H), 1.40 (t, 3 H).

Example 24

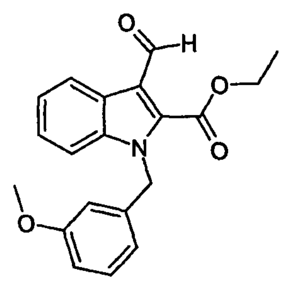
Ethyl 5-[2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)ethoxy]-1-(tetrahydro-2-furanylmethyl)-1*H*-indole-2-carboxylate



A solution of ethyl 5-[2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)ethoxy]-1*H*-indole-2-carboxylate **220** (40.7 mg, 0.100 mmol) in *N,N*-dimethylformamide (0.9 mL) was added to a stirred mixture of cesium carbonate (325 mg, 1.00 mmol) and 2-(bromomethyl)tetrahydrofuran (19.8 mg, 0.120 mmol) in *N,N*-dimethylformamide (2.4 mL). The reaction was stirred for 16 h and then the mixture was filtered though a plug (500 mg) of silica gel using ethyl acetate to rinse. The filtrate was concentrated *in vacuo* and then reverse phase preparative HPLC chromatography gave 19.8 mg of product (retention time = 2.4 min.). This material was taken to the next reaction without further purification or analysis.

Example 25

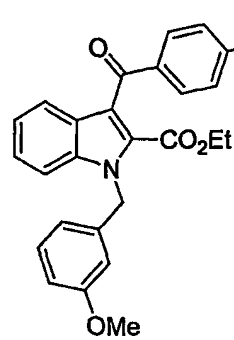
Ethyl 3-formyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Sodium hydride (60% dispersion in mineral oil, 2.40 g, 60.0 mmol) was cooled to 0 °C, and anhydrous methyl sulfoxide (75.0 mL, 1.06 mol) was added. The mixture was stirred at 0 °C for 15 minutes before a solution of ethyl 3-formyl-1H-indole-2-carboxylate (10.9 g, 50.2 mmol, Lit. *J. Heterocyclic Chem.* **1997**, *34*, 1431.) in 75 mL of methyl sulfoxide was added over a 20 minute period. The resulting solution was warmed to room temperature and stirred for 1 hour. 3-Methoxybenzylbromide (9.8 mL, 70.0 mmol) was added, and the solution was heated at 60 °C for 16 hours. The solution was cooled and poured into water (500 mL). The aqueous solution was extracted with ethyl acetate (3x), and the combined organic extracts were washed with 1 N hydrochloric acid (2x), water, and brine. The solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Trituration of the residue with 33% hexane/Et_2O provided the title compound as a solid (13.8 g, 81%). The product had: ^1H NMR (300 MHz, acetone-d_6) δ 10.61 (s, 1 H), 8.43 (d, 1 H), 7.61 (d, 1 H), 7.30-7.45 (m, 2 H), 7.19 (dd, 1 H), 6.80 (dd, 1 H), 6.63-6.74 (m, 2 H), 5.88 (s, 2 H), 4.48 (dq, 2 H), 3.70 (s, 3 H), 1.37 (t, 3 H); mass spectroscopy gave MH^+ = 338.1 (calc'd exact mass for $C_{20}H_{19}NO_4$ = 337.13).

Example 26

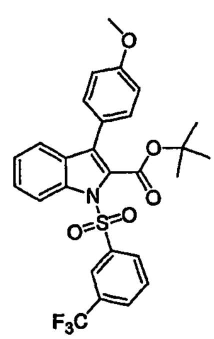
Ethyl 3-(4-methoxybenzoyl)-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Indole **203** (244 mg, 0.76 mmol) was added to a suspension of sodium hydride (36 mg, 0.91 mmol) in *N,N*-dimethylformamide (3 mL). After 10 min., sodium iodide (20 mg, 0.133 mmol) and 3-methoxybenzyl chloride (0.13 mL, 0.91 mmol) was added and the resulting mixture was stirred at rt. for ~15 h. Purification (silica gel chromatography 25:75 ethyl acetate:hexane) afforded 236 mg (70%) of Example **26**. Rf = 0.33 (75/25 hexane/ethyl acetate); LRMS (+esi) obs'd: 444.1; calc'd 443.17.

Example 27

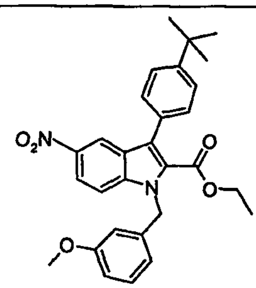
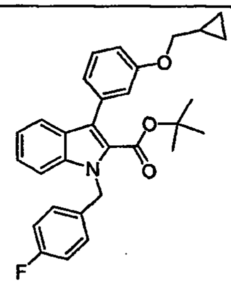
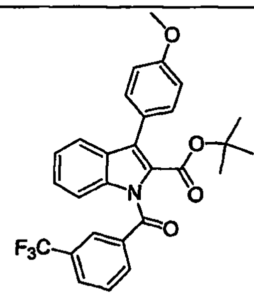
tert-Butyl 3-(4-Methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]sulfonyl}indole-2-carboxylate

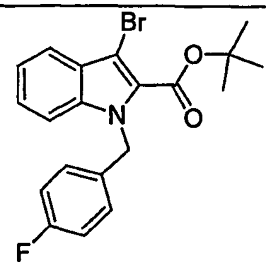
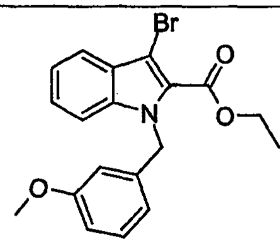
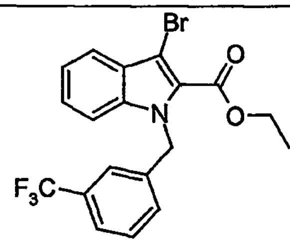
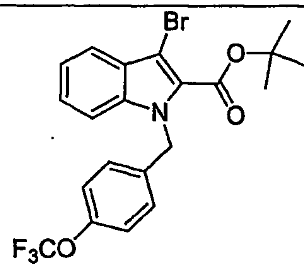
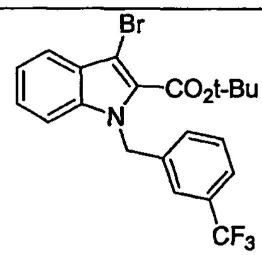


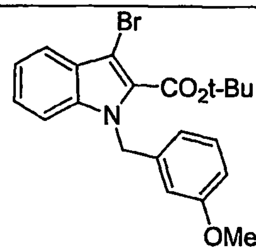
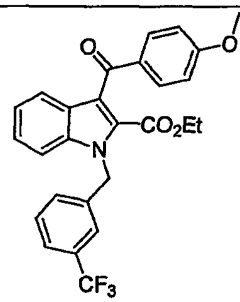
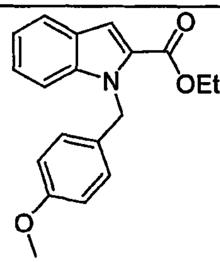
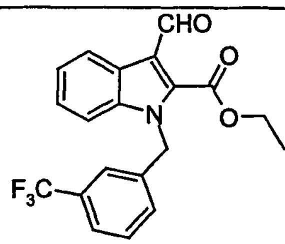
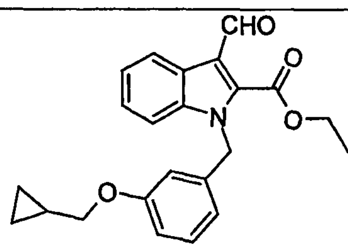
To a stirring solution of *tert*-butyl-3-(4-methoxyphenyl)indole-2-carboxylate (Example **105**, 75 mg, 0.23 mmol) in tetrahydrofuran (0.4 mL) was added potassium *tert*-butoxide (1 M in tetrahydrofuran, 0.4 mL) in one aliquot. After 10 minutes chloro[3-(trifluoromethyl)phenyl]sulfone (113 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature overnight. The resulting mixture was diluted with ethyl acetate (4 mL) and quenched with water (2 mL). The organic phase was extracted with ethyl acetate (3 x 4mL). The combined organic layers were dried over anhydrous

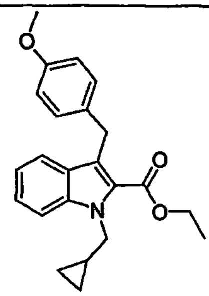
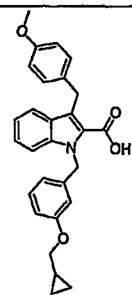
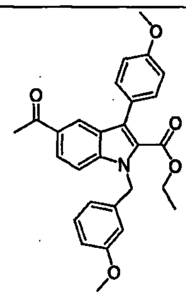
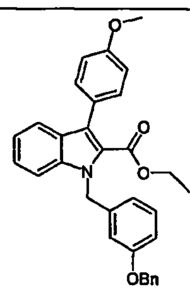
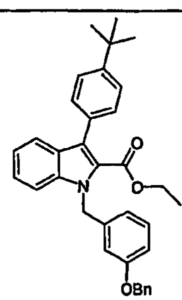
magnesium sulfate and concentrated under reduced pressure. The crude product was filtered through a plug of silica gel (30% ethyl acetate/hexane) to provide *tert*-butyl 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]sulfonyl}indole-2-carboxylate (45 mg, 37%), which was used in the next step without further purification.

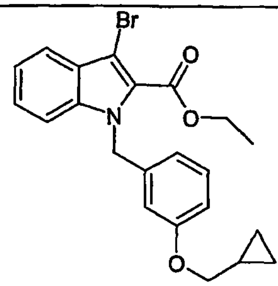
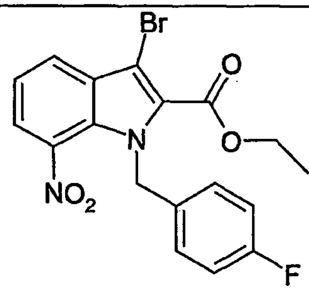
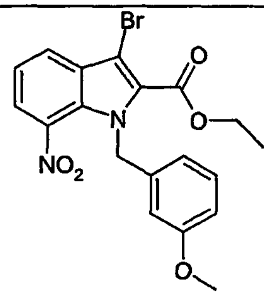
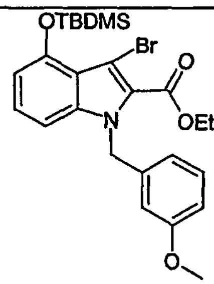
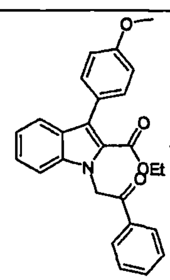
The following compounds were prepared according to the methods of Examples 22 - 27:

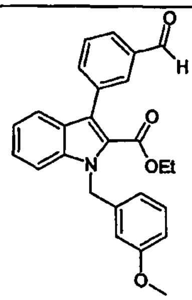
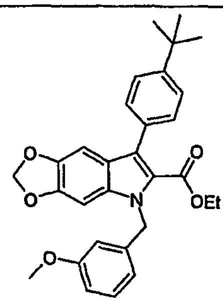
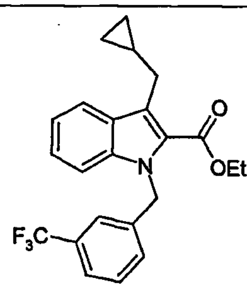
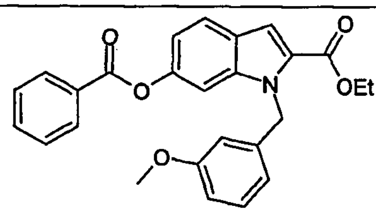
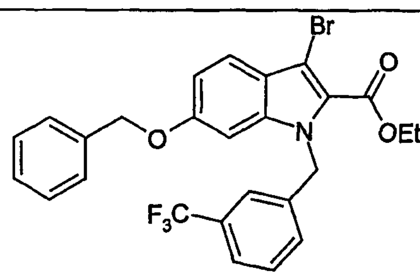
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
28		50			
29		44			
30		27			

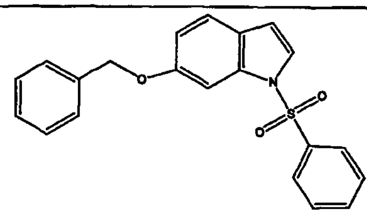
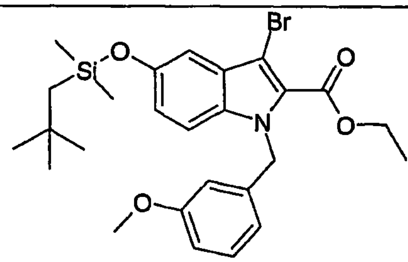
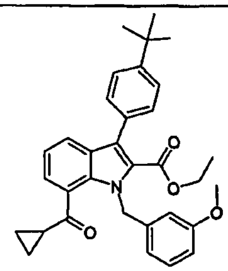
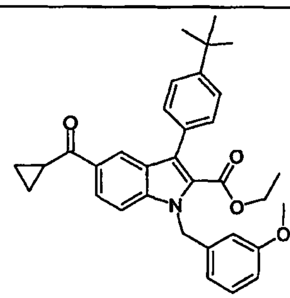
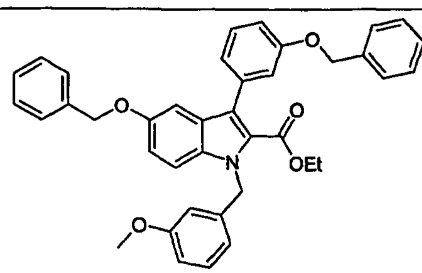
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
31		54			
32		73	390		
33		88	426	0.50 (hexane/ ethyl acetate 9:1)	
34		39			
35		crude			

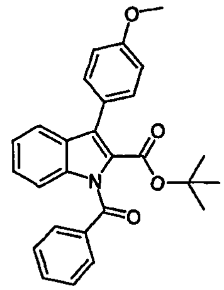
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
36		98	360.0	0.59 (Hexane/ ethyl acetate 7:1)	
37		96	482.1	0.38 (Hexane/ ethyl acetate 3:1)	
38		58	562.2	0.72 (Hexane/ ethyl acetate 4:1)	
40		80	376.1	0.31 (Hexane/ ethyl acetate 2:1)	
41		crude			

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
42		77		0.56 (Hexane/ ethyl acetate 4:1)	
43		76	598.2	0.48 (Hexane/ ethyl acetate 4:1)	
44		64		0.39 (Hexane/ ethyl acetate 4:1)	
45		100 crude			
46		100 crude			

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
47		51	428		
48		78	421		
49		58	433		
50		40		0.65 (Hexane/ ethyl acetate 3:1)	
51		100 crude			

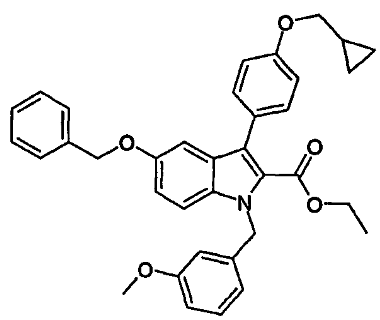
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
52		32			
53		55		0.53 (Hexane/ ethyl acetate 4:1)	
54		72	416.4	0.58 (Hexane/ ethyl acetate 9:1)	
55		34	432.4	0.60 (Hexane/ ethyl acetate 4:1)	
56		90	454.3	0.75 (Hexane/ ethyl acetate 7:3)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
57		88		0.55 (Hexane/ ethyl acetate 4:1)	
58		87			
59		71			
60		40			
227		75	598.2		

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
228		27 crude			

Example 61

Ethyl 5-(benzyloxy)-3-[4-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylate

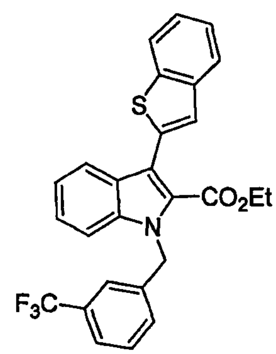


Example **5** (2.30 g, 12.0 mmol) and 2 M aqueous sodium carbonate (20 mL) were added to a stirred solution of ethyl 5-(benzyloxy)-3-bromo-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (4.03 g, 8.15 mmol) in EtOH (30 mL) and toluene (30 mL). Argon was bubbled through the mixture for 15 min and then tetrakis(triphenylphosphine)palladium(0) (1.15 g, 1.00 mmol) was added. The reaction was heated (85 °C) for 16 h and then cooled. The mixture was diluted with 1 M hydrochloric acid (200 mL) and then extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 60% dichloromethane/hexane gave 3.41 g (75%) of Example **61**. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95-7.48 (m, 13 H), 6.65-6.77 (m, 3 H), 5.76 (m, 2 H), 5.01 (s, 2 H), 4.13 (q, 2 H), 3.90 (d, 2 H), 3.74 (s, 3 H), 1.30-1.41 (s, 1 H), 1.05

(t, 3 H), 0.65-0.75 (m, 2 H), 0.38-0.45 (m, 2 H); mass spectroscopy gave $MH^+ = 562.2$ (calc'd exact mass for $C_{36}H_{35}NO_5 = 561.25$).

Example 62

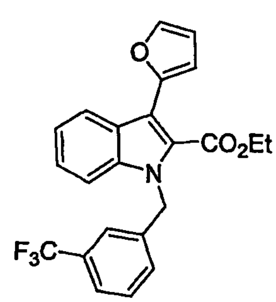
Ethyl 3-(benzothiozole)-1-(3-trifluoromethylbenzyl)-indole-2-carboxylate



A mixture of Example **33** (300 mg, 0.70 mmol), benzothiophene-2-boronic acid (195 mg, 1.1 mmol), 2N Na_2CO_3 (0.7 mL) and *N,N*-dimethylformamide (7 mL) was flushed with argon. $Pd(OAc)_2$ (16 mg, 0.07 mmol) and P(o-tolyl)$_3$ (43 mg, 0.14 mmol) were added and the mixture was heated at 100°C for ~15 h. The mixture was cooled and filtered through a short column of silica gel and sodium bicarbonate (elution with ethyl acetate). The filtrate was concentrated and the remaining oil was purified by flash chromatography (silica gel, 7:1 hexane:ethyl acetate) to afford 178 mg (53%) of Example **62** as a white solid. Rf = 0.51 (7/1 hexane/ethyl acetate); LRMS (+esi) obs'd: 480.0; calc'd 479.1.

Example 63

Ethyl 3-(2-furyl)-1-(3-trifluoromethylbenzyl)-indole-2-carboxylate

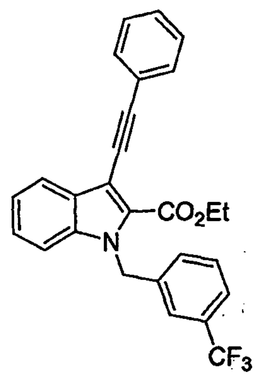


A mixture of Example **33** (300 mg, 0.70 mmol), 2-(tributylstannyl)furan (0.22 mL, 0.7 mmol), lithium chloride (30 mg, 0.7 mmol) and *N,N*-dimethylformamide (7 mL) was

flushed with argon. Tetrakis(triphenylphosphine) palladium (80 mg, 0.07 mmol) was added and the mixture was heated at 100°C for ~15 h. The mixture was cooled and filtered through a short column of silica gel (elution with ethyl acetate). The filtrate was washed with water and brine, concentrated and the remaining oil was purified by flash chromatography (silica gel, 7:1 hexane:ethyl acetate) to afford 160 mg (55%) of Example **63** as a white solid. Rf = 0.45 (7/1 hexane/ethyl acetate); LRMS (+esi) obs'd: 414.1; calc'd 413.1.

Example 64

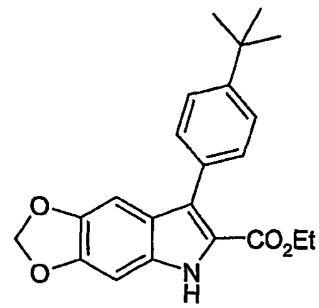
Ethyl 3-(2-phenylethynyl)-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate



A suspension/solution of Example **33** (500 mg, 1.17 mmol), phenyl acetylene (600 mg, 5.86mmol), triethyl amine (5.5 mL) in dry *N,N*-dimethylformamide (12 mL) was flushed with argon. Copper iodide (73 mg, 0.38 mmol) and Pd(dppf)$_2$Cl$_2$-dichloromethane (96 mg, 0.12 mmol) was added and again the system was flushed with Ar. The mixture was then heated at 79°C for 70 min. The suspension was filtered through Celite® (elution with ether) and the filtrate was washed water (3x 20 mL) and brine (20 mL). The ether layer was again filtered through silica to remove precipitates (elution with ether). The filtrate was concentrated and the remaining oil was purified by radial chromatography (4 mm silica gel plate, 95/5 hexane/ethyl acetate) to afford 23 mg (4%) of Example **64** as a brown solid. Rf = 0.23 (95/5 hexane/ethyl acetate).

Example 65

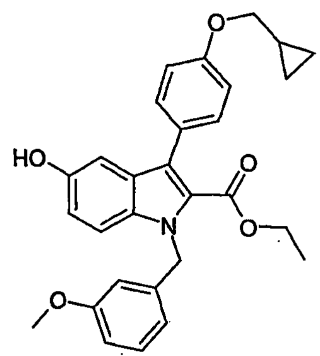
Ethyl 7-(4-tert-butylphenyl)-5H-[1,3]dioxolo[4,5]-findole-6-carboxylate



To a dry 100 mL round bottom flask and stir bar, purged with argon gas, was charged with 0.14g of $Pd_2(dba)_3$ and 0.14g trifurylphosphine followed by addition of 5 ml of toluene. The contents were stirred until homogeneous at which time a of ethyl 7-bromo-5H-[1,3]dioxolo[4,5-f]-indole-6-carboxylate (Example 19, 1.92 g, 6.13 mmol) in toluene (5 mL) was added to the catalyst solution via cannula. After approximately 10-15 minutes of stirring a 10 mL ethanol solution of 4-tert-butyl-phenyl boronic acid (1.64g, 9.2 mmol) to a stirring solution via cannula. This was followed by addition of 15mL of 2M sodium carbonate dropwise to the pot. The contents were heated to reflux overnight. The reaction was then quenched with 3 N hydrochloric acid and extracted with 3 times with 30 mL of ethyl acetate. The organic layer was then dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude material was purified via column chromatography yielding 1.24 g (55%) of a white solid (Rf- 0.38 20% ethyl acetate/hexane). The product had: ^{1}H NMR (300 MHz, acetone-D_6) 7.46 Hz (d, 1 H), 7.02 Hz (d, 1H) 6.97 Hz (d, 2H), 6.87 Hz (d, 2H), 5.99 Hz (d, 2H), 4.18 Hz (q, 2H), 1.35 Hz (s, 9H), 1.32 Hz (t, 3H).

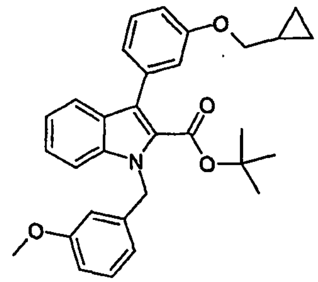
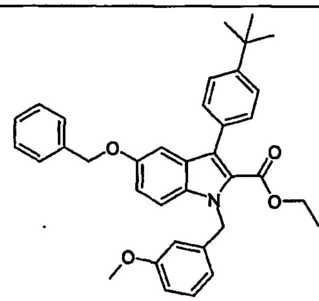
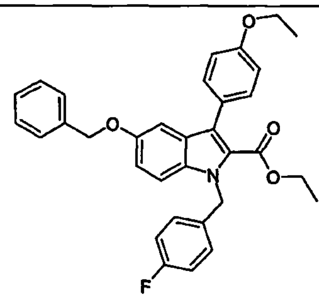
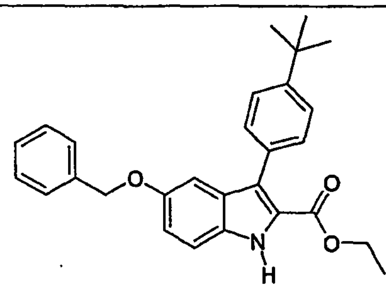
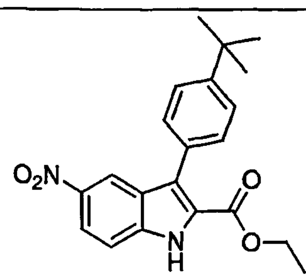
Example 66

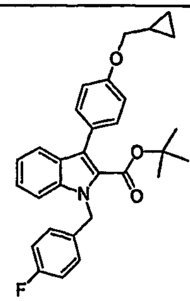
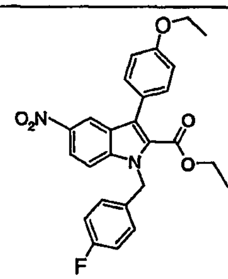
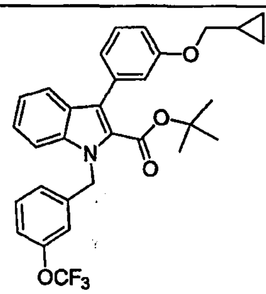
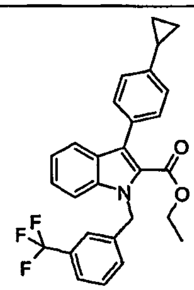
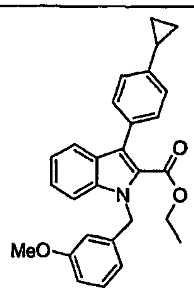
Ethyl 3-[4-(cyclopropylmethoxy)phenyl]-5-hydroxy-1-(3-methoxybenzyl)-1H-indole-2-carboxylate

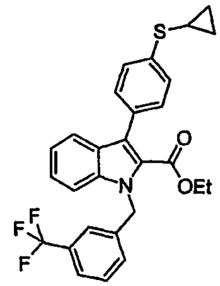
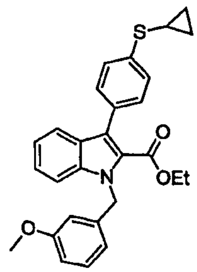
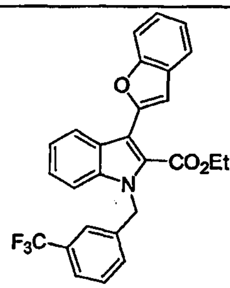
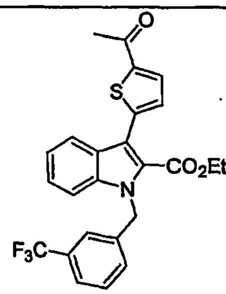
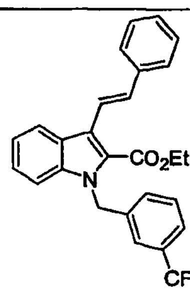


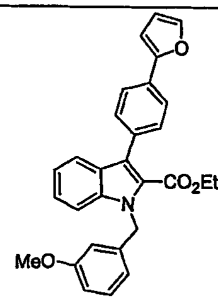
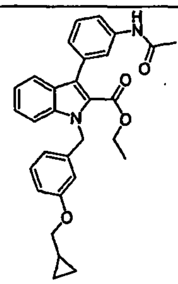
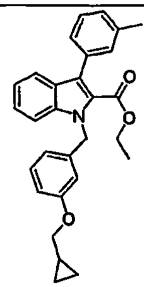
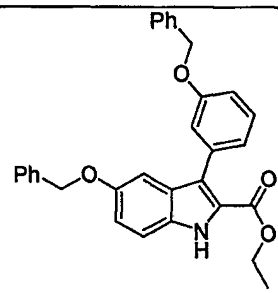
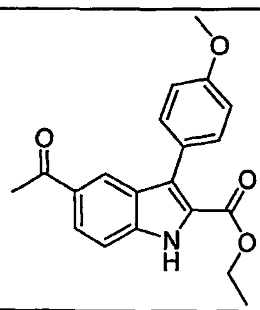
1-Bromo-4-cyclopropylmethoxy)benzene (2.30 g, 12.0 mmol) and 2 M aqueous sodium carbonate (20 mL) were added to a stirred solution of ethyl 5-(TBDMSO)-3-bromo-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **58**, 4.03 g, 8.15 mmol) in ethanol (30 mL) and toluene (30 mL). Argon was bubbled through the mixture for 15 min and then tetrakis(triphenylphosphine)palladium(0) (1.15 g, 1.00 mmol) was added. The reaction was stirred with heating (85 °C) for 16 h and then cooled. The mixture was diluted with 1 M hydrochloric acid (200 mL) and then extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (100 mL) and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 20 mL, 20 mmol) was added. The reaction was stirred for 1 h and then diluted with ethyl acetate (300 mL). The solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 20% ethyl acetate/hexane afforded 1.10 g (65%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.85 (s, 1 H), 7.28-7.37 (m, 3 H), 7.12 (dd, 1 H), 6.84-7.00 (m, 4 H), 6.61-6.74 (m, 3 H), 5.73 (s, 2 H), 4.09 (q, 2 H), 3.86 (d, 2 H), 3.67 (s, 3 H), 1.20-1.32 (m, 1 H), 0.84 (t, 3 H), 0.52-0.63 (m, 2 H), 0.31-0.41 (m, 2 H).

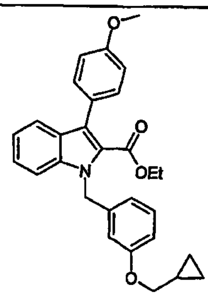
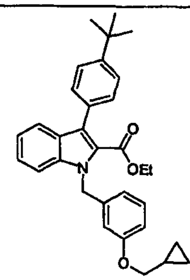
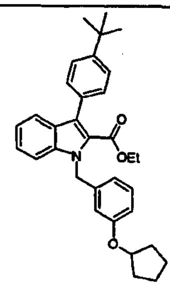
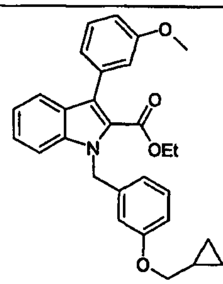
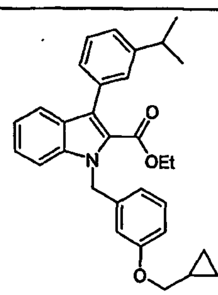
The following compounds were prepared according to the methods of Example **61 - 66**:

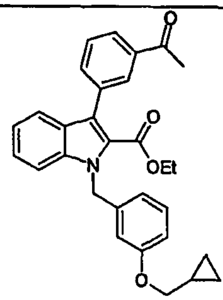
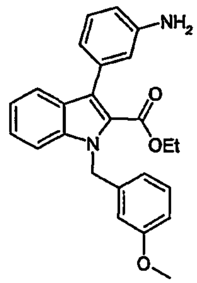
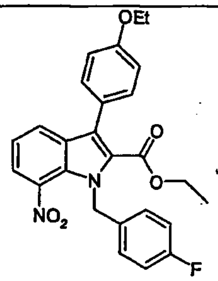
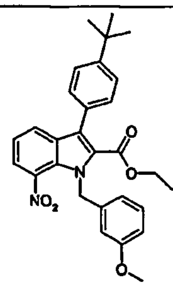
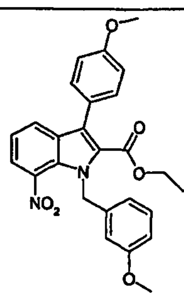
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
67		33	484.3		
68		86	548.2	0.82 (Hexane/ ethyl acetate 2:1)	
69		68	428.2	0.8 (Hexane/ ethyl acetate 2:1)	
70		68	428.2	0.80 (Hexane/ ethyl acetate 2:1)	
71		66		0.62 (Hexane/ ethyl acetate 2:1)	

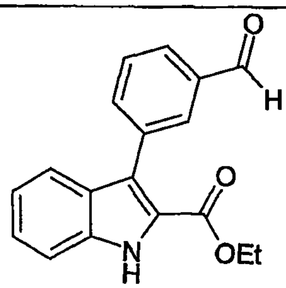
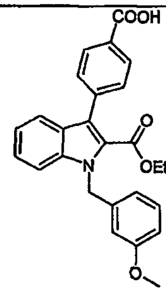
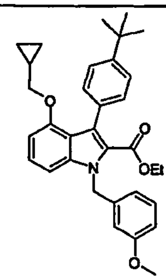
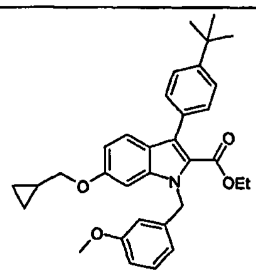
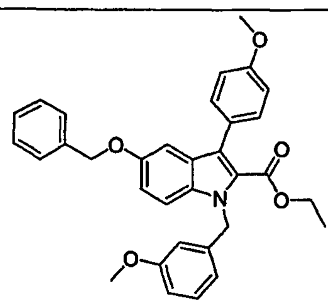
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
72		55			
73		73		0.71 (Hexane/ ethyl acetate 2:1)	
74		43			
75		50	464		
76		56	426		

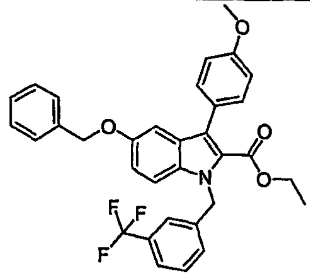
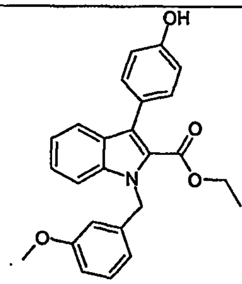
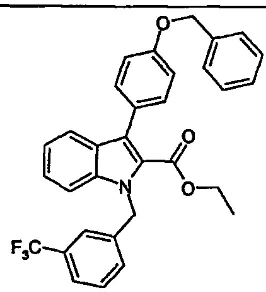
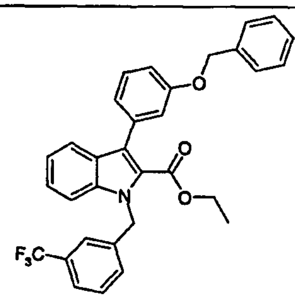
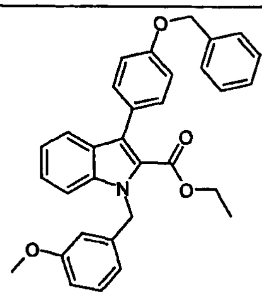
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
77		71	496		
78		67	458		
79		25		0.53 (Hexane/ ethyl acetate 7:1)	
80		62	472.2	0.3 (Hexane/ ethyl acetate 7:1)	
81		crude	450.1	0.26 (Hexane/ ethyl acetate 95:5)	

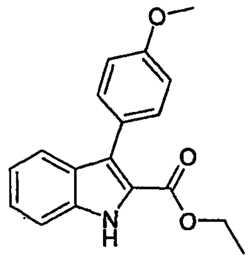
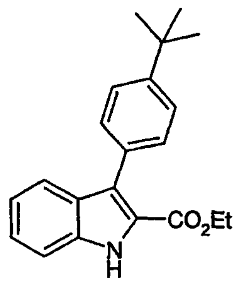
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
82		88	452.2	0.49 (hexane/ ether 8:2)	
83		61	483.1	0.31 (Hexane/ ethyl acetate 1:1)	
84		crude	440.2	0.45 (Hexane/ ethyl acetate 9:1)	
85		67	478.1	0.32 (Hexane/ ethyl acetate 4:1)	
86		45		0.24 (Hexane/ ethyl acetate 4:1)	

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
87		74			
88		68			
89		80			
90		100		0.56 (Hexane/ ethyl acetate 4:1)	
91		100		0.71 (Hexane/ ethyl acetate 4:1)	

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
92		57	468	0.50 (Hexane/ ethyl acetate 3:1)	
93		62		0.50 (Hexane/ ethyl acetate 2:1)	
94		75	463		
95		79			
96		100	461		

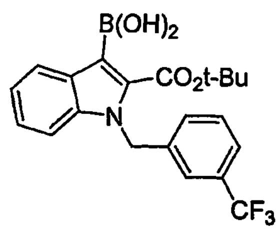
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
97		73	294 (M^+) GC-MS		
98		64			
99		50			
100		27	512.7	0.7 (Hexane/ ethyl acetate 4:1)	
101		69	522.8		

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
102		74	560.1	0.36 (Hexane/ ethyl acetate 6:1)	
121		77	402		
225		77			
226		72			
103		86	492		

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
105		53			
224		93		0.50 (Hexane/ ethyl acetate 4:1)	

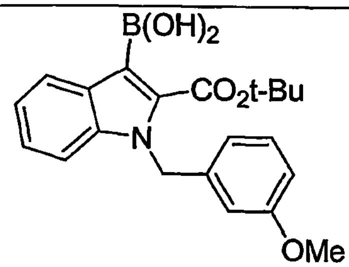
Example 106

2-*tert*-Butoxycarbonyl) 1-[3-(trifluoromethyl)benzyl]-indole-3-yl boronic acid



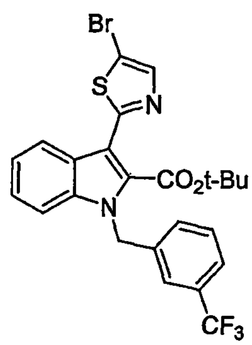
A solution of butyllithium in hexane (7.10 mL, 1.6 M) was added to a –78°C solution of Example **35** (4.95 gm, 10.9 mmol) in tetrahydrofuran (30 mL). After 5 min., trimethyl borate (3.72 mL, 32.7 mmol) was added and the mixture was allowed to warm to rt. over 2 h. 2N hydrochloric acid (30 mL) was added and the mixture was vigorously stirred for 30 min. Ethyl acetate was added and the layers were separated. The organic layer was dried and concentrated. Trituration of the remaining oil with ether followed by drying under reduced pressure afforded 2.3 g (50%) of Example **106** as a white solid. Rf = 0.29 (4/1 hexane/ethyl acetate).

The following compounds were prepared according to the methods of Example **106**:

Ex. No.	Structure	Yield [%]	MS [M+H⁺]	Rf	mp [°C]
108		44		0.28 (Hexane/ethyl acetate 4:1)	

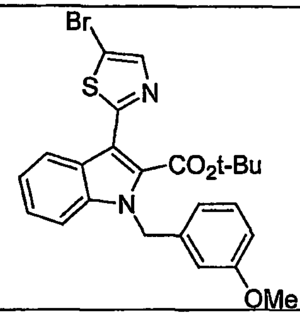
Example 109

***tert*-Butyl 3-(5-bromo-1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylate**



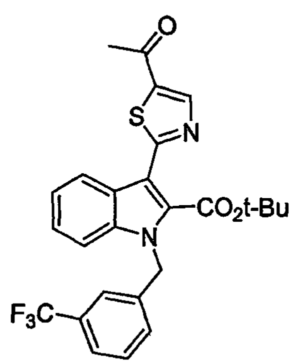
To a solution of Example **106** (150 mg, 0.36 mmol) and Example **4** (68 mg, 0.28 mmol) in toluene (0.7 mL) and ethanol (0.7 mL) was added aq. Na_2CO_3 (0.36 mL, 2N). The reaction vessel was flushed with Ar for 10 min. Tetrakis(triphenylphosphine)-palladium (34 mg, 0.029 mmol) was added and the mixture was heated at 85°C until the disappearance of the boronic acid. The mixture was cooled and filtered. The filtrate was concentrated and the remaining oil was purified by flash chromatography (silica gel, 7:1 hexane:ethyl acetate) to afford 100 mg (66%) of Example **109** as a yellow solid. Rf = 0.61 (7/1 hexane/ethyl acetate); LRMS (+esi) obs'd: 536.8; calc'd 536.0.

The following compounds were prepared according to the method of Example **109**:

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
110		43	498.9	0.72 (Hexane/ethyl acetate 4:1)	

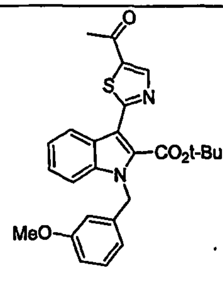
Example 111

***tert*-Butyl 3-(5-acetyl-1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylate**



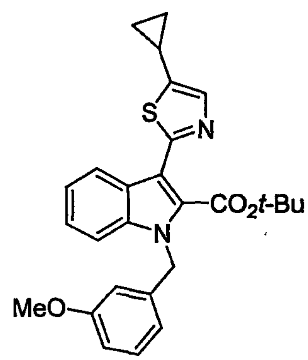
A mixture of Example **108** (300 mg, 0.56 mmol), $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) and lithium chloride (80 mg, 1.68 mmol) in tetrahydrofuran (2 mL) and toluene (2 mL) was flushed with argon. 1-Ethoxyvinyl tri-*n*-butylstannane (224 mg, 0.62 mmol) was added and the mixture was heated at 90 °C for 4 h. A second portion of stannane (107 mg, 0.30 mmol) was added and heating was continued for 1 h. The mixture was cooled to rt. and 10% hydrochloric acid (2 mL) was added. The mixture was stirred for 1 h. The mixture was washed with water, dried and concentrated. The oil thus obtained was purified by flash chromatography (silica gel, 5:1 hexane:ethyl acetate) to afford 280 mg of slightly impure Example **111** which was used without further purification. LRMS (+esi) obs'd: 500.9; calc'd 500.1.

The following compounds were prepared according to the method of Example **111**:

Ex. No.	Structure	Yield [%]	MS [M+H⁺]	Rf	mp [°C]
111A		crude	463.0	0.32 (Hexane/ethyl acetate 5:1)	

Example 112

tert-Butyl 3-(5-cyclopropyl-1,3-thiazol-2-yl)-1-(3-methoxybenzyl)-indole-2-carboxylate



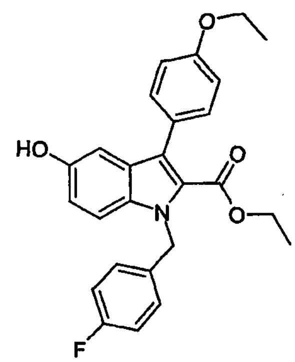
Cyclopropyl boronic acid: A solution of *t*-butyllithium in hexane (17.0 mL, 25.4 mmol) was added to a –78°C solution of cyclopropyl bromide (1.51 gm, 12.4 mmol) in dry tetrahydrofuran (20 mL). After stirring for 15 min., trimethoxy borate (1.23 gm, 11.8 mmol) was added and the resulting mixture was warmed to rt. over 1h. 2N HCl (15 mL) was added and the aq. phase was extracted with ethyl acetate. The extracts were dried over anhydrous sodium sulfate and concentrated to give the cyclopropyl boronic which was used in the coupling step without further purification.

A mixture of cyclopropyl boronic acid (75 mg, 0.84 mmol), Example **110** (200 mg, 0.42 mmol), Na_2CO_3 (2N, 0.9 mL), and *N,N*-dimethylformamide (3.5 mL) was flushed with argon. Palladium(II) acetate (18 mg, 0.08 mmol) and P(o-tolyl)$_3$ (50 mg, 0.16 mmol) were added and the mixture was heated at 100°C for 1 h. The mixture was cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried

over anhydrous sodium sulfate and concentrated. Purification of the remaining oil by flash chromatography gave slightly impure Example **112** which was used without further purification. LRMS (+esi) obs'd: 461.0; calc'd 460.2.

Example 113

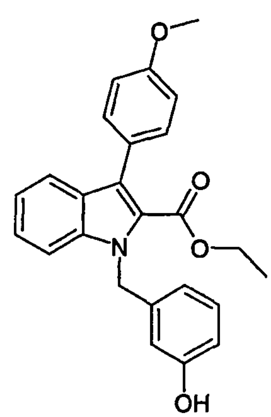
Ethyl 3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-5-hydroxy-1*H*-indole-2-carboxylate



A solution of ethyl 5-(benzyloxy)-3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-1*H*-indole-2-carboxylate (Example **69**, 4.7 g, 9.0 mmol) in ethyl acetate (15 mL) was added to a suspension of 10% palladium on charcoal (2.0 g) in ethyl acetate (10 mL). The mixture was placed under an atmosphere of hydrogen (1 atm) and stirred for 16 h. The reaction was filtered through a pad of Celite using ethyl acetate to rinse. Evaporation of the filtrate left 3.5 g (90%) of the desired product. The product had: ^1H NMR (300 MHz, acetone-D_6) δ 7.98 (s, 1 H), 6.89-7.42 (m, 11 H), 5.81 (s, 2 H), 4.03-4.19 (m, 4 H), 1.41 (t, 3 H), 1.04 (t, 3 H).

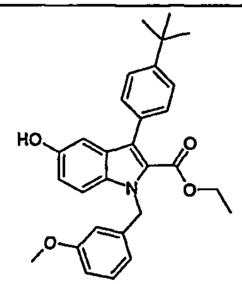
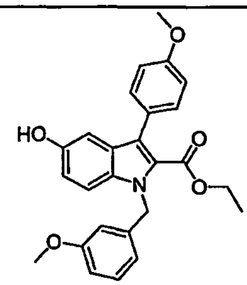
Example 114

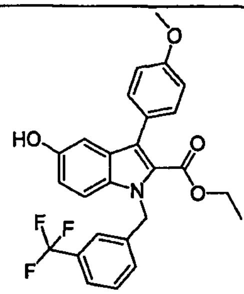
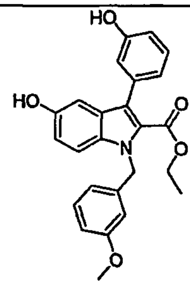
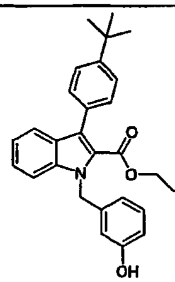
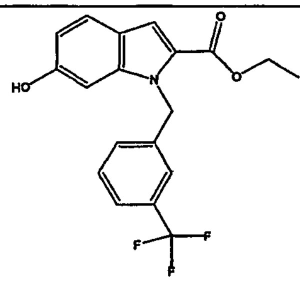
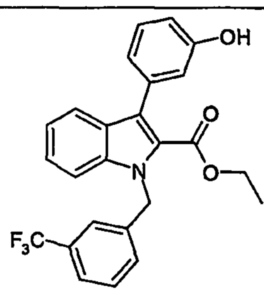
Ethyl 1-[(3-hydroxyphenyl)methyl]-3-(4-methoxyphenyl)indole-2-carboxylate

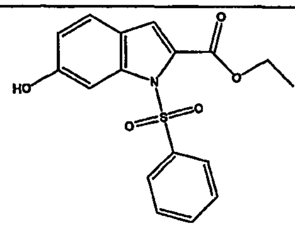


To a Parr shaker bottle purged with Argon was added palladium on carbon (Degussa type) (500 mg), ethyl acetate (10 mL), ethyl 3-(4-methoxyphenyl)-1-{[3-(phenylmethoxy)phenyl]methyl}indole-2-carboxylate (Example **45**, 5 g crude material, 7.0 mmol, in 120 mL methanol and 40 mL ethyl acetate). The mixture was hydrogenated at 55 psi for 48 h. The mixture was then filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified with silica gel flash chromatography using hexane/ethyl acetate (3/1 to 2/1) to give ethyl 1-[(3-hydroxyphenyl)methyl]-3-(4-methoxyphenyl)indole-2-carboxylate as a light yellow oil (2.5 g, 89%): MS (M^+) calcd for $C_{25}H_{23}NO_4$ 401.1, found 401.0; ^{1}H NMR ($CDCl_3$) δ 7.60 (dd, J = 8.1 Hz, 1H), 7.30-7.45 (m, 4H), 7.13-7.21 (m, 2H), 6.98 (d, J = 8.1 Hz, 2H), 6.64-6.78 (m, 2H), 6.52 (s, 1H), 5.77 (s, 2H), 4.14 (q, J = 7.0 Hz, 2H), 1.04 (t, J = 7.0 Hz, 3H).

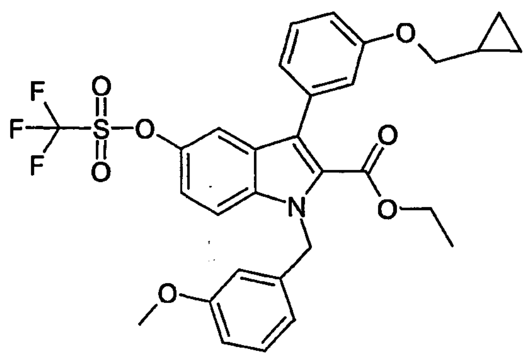
The following compounds were prepared according to the method of Example **114**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
115		93	458.2	0.67 (Hexane/ethyl acetate 2:1)	
116		97	432.1	0.35 (Hexane/ethyl acetate 2:1)	

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
117		92	470.1	0.41 (Hexane/ethyl acetate 2:1)	
118		100	417.2	0.22 (Hexane/ethyl acetate 2:1)	
119		56			
120		63			
122		86			

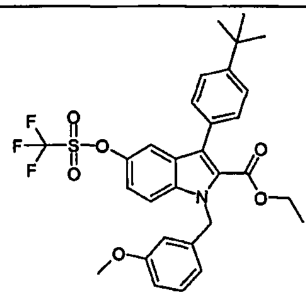
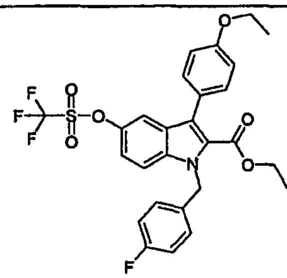
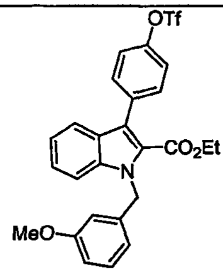
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
123		96		0.19 (Hexane/ethyl acetate 4:1)	

Example 124
Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-{[(trifluoromethyl) sulfonyl]oxy}-1*H*-indole-2-carboxylate



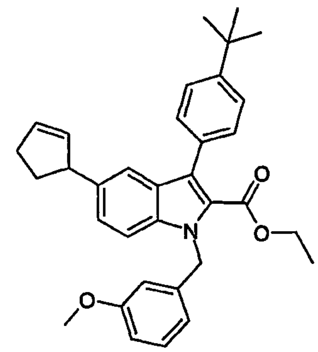
Triflic anhydride (0.84 mL, 1.4 g, 5.0 mmol) and dimethylaminopyridine (25 mg, 0.20 mmol) were added to a cooled (0 °C) and stirred solution of ethyl 3-[3-(cyclopropylmethoxy)phenyl]-5-hydroxy-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **66**, 1.00 g, 2.12 mmol) in dichloromethane (10 mL) and pyridine (2 mL). The reaction was warmed to rt and then stirred an additional 2 h. The solution was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 15% ethyl acetate/hexane afforded 1.14 g (89%) of desired product. The product had: ^{1}H NMR (300 MHz, acetone-D$_6$) δ 7.73 (d, 1 H), 7.54 (d, 1 H), 7.35-7.42 (m, 3 H), 7.20 (dd, 1 H), 7.00-7.07 (m, 2 H), 6.68-6.83 (m, 3 H), 5.88 (s, 2 H), 4.16 (q, 2 H), 3.91 (d, 2 H), 3.72 (s, 3 H), 1.25-1.35 (m, 1 H), 10.5 (t, 3 H), 0.55-0.65 (m, 2 H), 0.32-0.42 (m, 2 H); mass spectroscopy gave M$^+$ = 603.1 (exact mass calc'd for $C_{20}H_{28}F_3NO_7S$ = 603.15).

The following compounds were prepared according to the method of Example 124:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
125		96			
126		52			
127		48	533.9		

Example 128

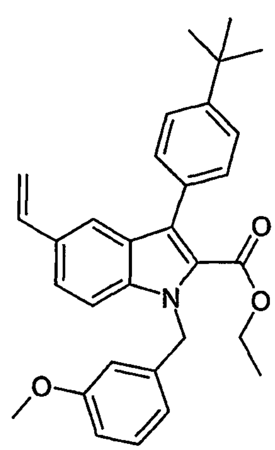
Ethyl 3-(4-*tert*-butylphenyl)-5-(2-cyclopenten-1-yl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Cyclopentene (0.44 mL, 341 mg, 5.0 mmol), palladium acetate (22 mg, 0.10 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol) and potassium acetate (295 mg, 1.0 mmol) were added to a stirred solution of ethyl 3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-5-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-indole-2-carboxylate (Example **125**, 570 mg, 1.0 mmol) in *N,N*-dimethylformamide (5 mL). The reaction was stirred for 48 h and then diluted with ethyl acetate (100 mL). The solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 6:1 ethyl acetate/hexane gave 230 mg, (45%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.49-7.56 (m, 3 H), 7.37-7.43 (m, 3 H), 7.17-7.23 (m, 2 H), 6.68-6.92 (m, 3 H), 4.09 (q, 3 H), 3.92-4.01 (m, 1 H), 3.75 (s, 3 H), 2.31-2.50 (m, 3 H), 1.62-1.77 (m, 1 H), 1.39 (s, 9 H), 0.98 (t, 3 H).

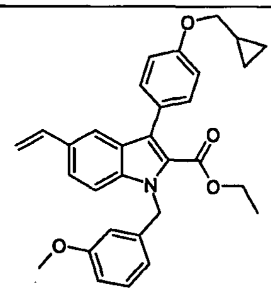
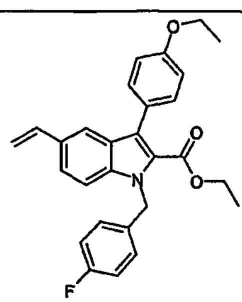
Example 129

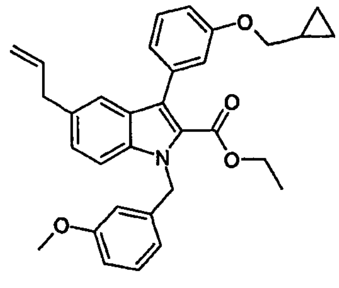
Ethyl 3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-5-vinyl-1*H*-indole-2-carboxylate



Lithium chloride (297 mg, 7.0 mmol) and tributylvinyl tin (0.43 mL, 467 mg, 1.5 mmol) were added to a stirred solution of ethyl 3-(4-tert-butylphenyl)-1-(3-methoxybenzyl)-5-{[(trifluoromethyl)sulfonyl]oxy}-1H-indole-2-carboxylate (Example **125**, 570 mg, 0.995 mmol) in tetrahydrofuran (10 mL). Argon was bubbled through the mixture for 10 min and then tetrakis(triphenylphospine)palladium (115 mg, 0.10 mmol) was added. The reaction was heated (67 °C for 18 h and then cooled to rt. The mixture was diluted with ethyl acetate (100 mL) and then washed successively with water, 10% aqueous ammonium hydroxide, water and brine. The organic solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 10% ethyl acetate/hexane gave 334 mg (72%) of the desired product. The product had: ^1H NMR (300 MHz, $CDCl_3$) δ 7.14-7.58 (m, 8 H), 6.64-6.82 (m, 4 H), 5.77 (s, 2 H), 5.65 (dd, 1 H), 5.13 (dd, 1 H), 4.10 (q, 2 H), 3.73 (s, 3 H), 1.40 (s, 9 H), 0.95 (t, 3 H); mass spectroscopy gave MH^+ = 468.2 (calc'd exact mass for $C_{31}H_{33}NO_3$ = 467.25).

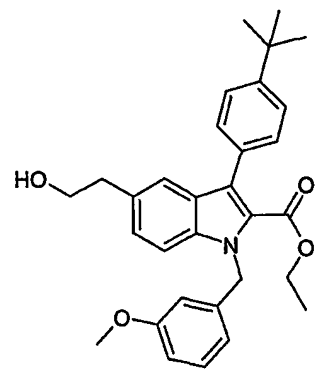
The following compounds were prepared according to the method of Examples **128 – 129:**

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
130		3	482.1	0.48 (Hexane/ethyl acetate 4:1)	
131		69		0.41 (Hexane/ethyl acetate 5:1)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
132		82	496.2		

Example 133

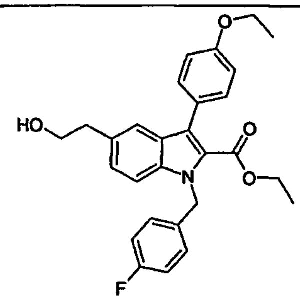
Ethyl 3-(4-*tert*-butylphenyl)-5-(2-hydroxyethyl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Acetic acid (63 µL, 66 mg, 1.1 mmol) was added slowly to a cooled (0 °C) and stirred slurry of sodium borohydride (41.6 mg, 1.10 mmol) in tetrahydrofuran (2 mL). The mixture was stirred for 1 h and then a solution of ethyl 3-(4-tert-butylphenyl)-1-(3-methoxybenzyl)-5-vinyl-1*H*-indole-2-carboxylate (Example **129**, 430 mg, 0.920 mmol) in tetrahydrofuran (5 + 2 mL rinse) was added. The reaction was stirred overnight and then cooled (0 °C). The reaction was quenched by successive addition of EtOH (6 mL), 6 M aqueous sodium acetate (5 mL) and 27% aqueous hydrogen peroxide (5 mL). The mixture was heated (50 °C) for 1 h and then cooled. The reaction was diluted with water (100 mL) and then extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 30% ethyl acetate/hexane afforded 325 mg (75%) of desired product. The product had: ^{1}H

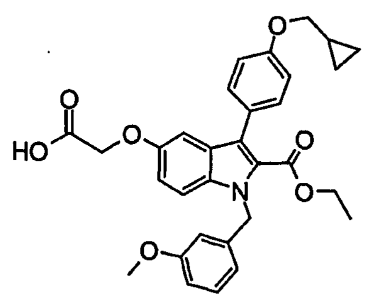
NMR (300 MHz, $CDCl_3$) δ 7.28-7.48 (m, 6 H), 7.15-7.22 (m, 2 H), 6.75 (dd, 1 H), 6.64-6.72 (m, 2 H), 7.76(s, 2 H), 4.08 (q, 2 H), 3.78-4.00 (m, 3 H), 3.73 (s, 3 H), 2.91 (t, 2 H), 1.39 (s, 9 H), 0.95 (t, 3 H).

The following compounds were prepared according to the method of Example **133**

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
134		56	462.2		

Example 135

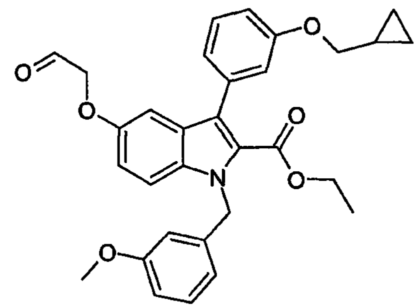
{[3-[4-(Cyclopropylmethoxy)phenyl]-2-(ethoxycarbonyl)-1-(3-methoxybenzyl)-1*H*-indol-5-yl]oxy}acetic acid



Formic acid (1 mL) was added to a stirred solution of ethyl 5-(2-*tert*-butoxy-2-oxoethoxy)-3-[4-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **150**, 20 mg, 0.035 mmol) in dichloromethane (1 mL). The reaction was stirred for 1 h and then concentrated *in vacuo*. Flash chromatography of the residue over silica gel using (1:1 ethyl acetate/hexane) gave 10 mg (53% of the desired product. The product had: ^{1}H NMR (300 MHz, CD_3OD) δ 7.30-7.48 (m, 3 H), 6.92-7.19 (m, 4 H), 6.77 (dd, 1 H), 6.54-6.68 (m, 3 H), 5.79 (s, 2 H), 4.61 (s, 2 H), 4.13 (q, 2 H), 3.95 (d, 2 H), 3.74 (s, 3 H), 1.29-1.41 (m, 1 H), 1.25 (t, 3 H), 0.61-0.71 (m, 2 H), 0.39-0.49 (m, 2 H); mass spectroscopy gave MH+ of 530.2 (calc'd exact mass for $C_{31}H_{31}NO_7$ = 529.21).

Example 136

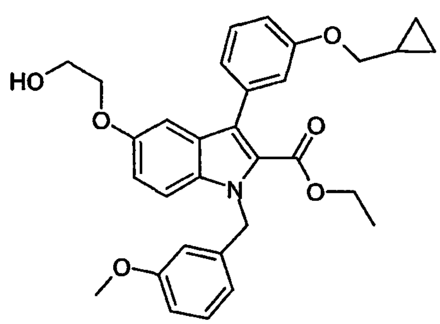
Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-(2-oxoethoxy)-1*H*-indole-2-carboxylate



Sodium periodate (812 mg, 3.80 mmol) and osmium tetroxide (2.5 wt% solution in *tert*-butanol, 1.2 mL, 0.10 mmol) were added to a stirred solution of ethyl 3-[4-(cyclopropyl-methoxy)phenyl]-1-(3methoxy-benzyl)-5-allyloxy-1*H*-indole-2-carboxylate (Example **149**, 640 mg, 1.25 mmol) in tetrahydrofuran (15 mL) and water (1.5 mL). The reaction was stirred for 16 h and then diluted with water (100 mL). The product was extracted with ethyl acetate (3x50 mL) and then the combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo.* Flash chromatography of the residue over silica gel using 8:1 hexane/ethyl acetate gave 395 mg (62%) of product containing impurities. The material was used in the next reaction without further purification or analysis.

Example 137

Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-5-(2-hydroxyethoxy)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate

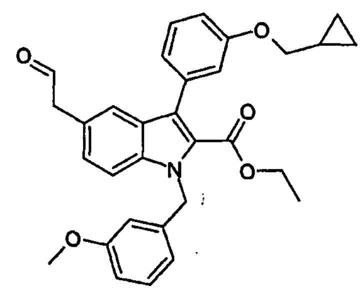


Sodium borohydride (38 mg, 1.0 mmol) was added to a stirred solution of ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-(2-oxoethoxy)-1*H*-indole-2-carboxylate (Example **136**, 380 mg, 0.74 mmol) in methanol (10 mL). The reaction was

stirred for 2 h and then the reaction was quenched with water (100 mL). The product was extracted with ethyl acetate (3x40 mL) and then the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to leave 363 mg (95%) of product containing some impurities. The material was used in the next reaction without further purification. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.34-7.46 (m, 3 H), 7.16 (dd, 1 H), 6.93-7.02 (m, 4 H), 6.65-6.81 (m, 3 H), 5.78 (s, 2 H), 3.82-4.23 (m, 9 H), 3.69 (s, 3 H), 1.24-1.34 (m, 1 H), 1.02 (t, 3 H), 0.60-0.70 (m, 2 H), 0.34-0.44 (m, 2 H).

Example 138

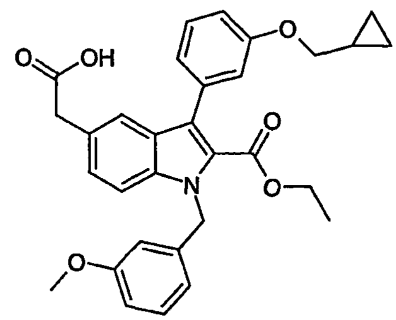
Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl) -5-(2-oxoethyl)-1*H*-indole-2-carboxylate



Sodium periodate (430 mg, 2.0 mmol) and osmium tetroxide (2.5 wt% solution in *tert*-butanol, 0.50 mL, 0.05 mmol) were added to a stirred solution of ethyl 5-allyl-3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **132**, 385 mg, 0.777 mmol) in tetrahydrofuran (10 mL) and water (1 mL). The reaction was stirred for 18 h and then diluted with water (100 mL). The product was extracted with ethyl acetate (3x50 mL) and then the combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 15% ethyl acetate/hexane gave 183 mg (47%) of product containing impurities. The material was used in the next reaction without further purification. Mass spectroscopy gave MH^+ = 498.1 (exact mass calc'd for $C_{31}H_{31}NO_5$ = 497.22).

Example 139

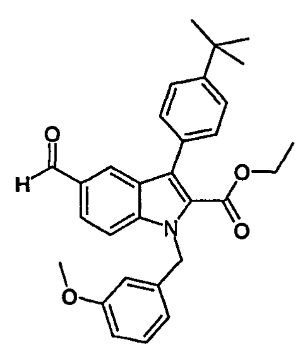
[3-[3-(Cyclopropylmethoxy)phenyl]-2-(ethoxycarbonyl)-1-(3-methoxybenzyl)-1H-indol-5-yl]acetic acid



2-Methyl-2-butene (2 mL), sodium phosphate monobasic (307 mg, 2.6 mmol) and sodium perchlorate (307 mg, 3.4 mmol) were added to a stirred solution of ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-(2-oxoethyl)-1*H*-indole-2-carboxylate (Example **138**, 169 mg, 0.34 mmol) in *tert*-butanol (8 mL) and water (3 mL). The reaction was stirred for 24 h and then diluted with ethyl acetate (100 mL). The solution was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 60% ethyl acetate/hexane afforded 35 mg (20%) of the product. The product had: ^{1}H NMR (300 MHz, acetone-D$_6$) δ 6.96-7.57 (m, 8 H), 6.58-6.80 (m, 3 H), 5.83 (s, 2 H), 4.11 (q, 2 H), 3.90 (d, 2 H), 3.70 (s, 3 H), 3.67 (s, 2 H), 1.24-1.40 (m, 1 H), 1.03 (t, 3 H), 0.55-0.65 (m, 2 H), 0.35-0.46 (m, 2 H); mass spectroscopy gave M-H$^+$ = 512.5 (calc'd exact mass for $C_{31}H_{31}NO_6$ = 513.22).

Example 140

Ethyl 3-(4-*tert*-butylphenyl)-5-formyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate

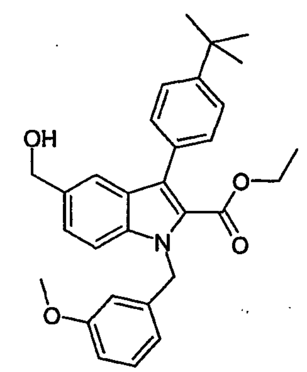


Ethyl 3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-5-vinyl-1H-indole-2-carboxylate (Example **129**, 2.28 g, 4.9 mmol) was dissolved in anhydrous tetrahydrofuran

(25 mL), and osmium tetroxide (2.5 weight % solution in 2-methyl-2-propanol, 1.5 mL, 0.15 mmol) was added. After ten minutes, the reaction mixture was cooled with an ice bath. Sodium periodate (2.10 g, 9.8 mmol) was added followed by a minimum volume of water to dissolve the solids. The reaction was allowed to return to room temperature, and after 30 minutes, the reaction was partitioned between water and diethyl ether. The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated. The resulting crude oil was passed through a pad of silica gel with 20% ethyl acetate/hexane. The filtrate was concentrated *in vacuo* without heat to provide the title compound as a brown oil (1.70g, 75%). The product had: ^{1}H NMR (300 MHz, acetone-d_6) 10.01 (s, 1 H), 8.15 (d, 1 H), 7.88 (d, 1 H), 7.75 (d, 1 H), 7.54 (d, 2 H), 7.44 (d, 2 H), 7.21-7.19 (m, 1 H), 6.81-6.79 (m, 1 H), 6.72-6.69 (m, 2 H), 5.92 (s, 2 H), 4.12 (q, 2 H), 3.71 (s, 3 H), 1.39 (s, 9 H), 0.78 (t, 3 H).

Example 141

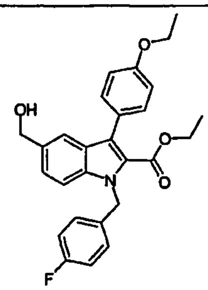
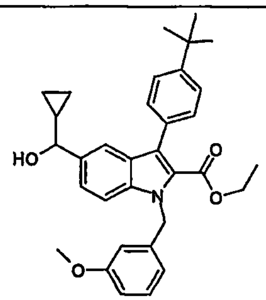
Ethyl 3-(4-*tert*-butylphenyl)-5-(hydroxymethyl)-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Ethyl 3-(4-*tert*-butylphenyl)-5-formyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **140**, 700 mg, 1.493 mmol) was dissolved in ethanol (15 mL) and cooled to 0 °C. Sodium borohydride (57 mg, 1.50 mmol) was added, and the solution was stirred for 1 hour. Water (27 µL, 1.5 mmol) was added, and the mixture was allowed to warm to room temperature. The mixture was concentrated via rotary evaporation, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The resulting crude oil was purified by flash chromatography on silica gel eluted with hexane then 20% ethyl acetate/hexane. The title compound was collected as a foam (530 mg, 75%). The product had: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.56-7.55 (m, 1 H), 7.53-7.51

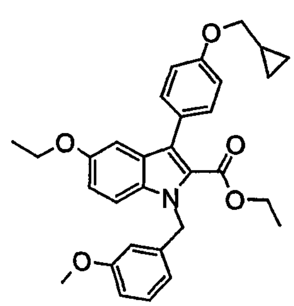
(m, 1 H), 7.50-7.47 (m, 2 H), 7.41-7.39 (m, 1 H), 7.37-7.34 (m, 2 H), 7.18-7.16 (m, 1 H), 6.77-6.75 (m, 1 H), 6.68-6.70 (m, 2 H), 5.85 (s, 2 H), 4.65 (d, 2 H), 4.09 (q, 2 H), 4.06-4.04 (m, 1 H), 3.70 (s, 3 H), 1.38 (s, 9 H), 0.96 (t, 3 H); mass spectroscopy gave MH^+ = 472.2 (calc'd exact mass for $C_{30}H_{33}NO_4$ = 471.24).

The following compounds were prepared according to the method of Example **141**:

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
142		97	448.1		
143		crude			

Example 144

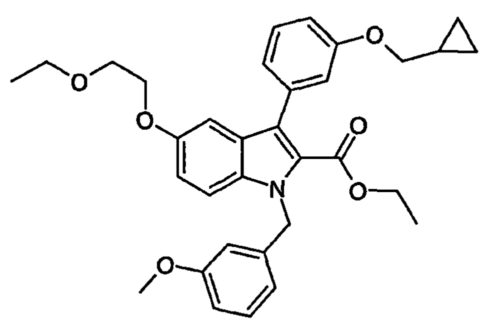
Ethyl 3-[4-(cyclopropylmethoxy)phenyl]-5-ethoxy-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Iodoethane (468 mg, 3.0 mmol) and powdered potassium carbonate (138 mg, 1.0 mmol) was added to a solution of ethyl 3-[4-(cyclopropylmethoxy)phenyl]-5-hydroxy-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **66**, 120 mg, 0.25 mmol) in DMF (5 mL). The mixture was heated (50 °C) for 16 h and then cooled. The resulting mixture was diluted with ethyl acetate (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by preparative TLC using 4:1 ethyl acetate/hexane as the eluant, to afford 52 mg (42%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.42 (d, 1 H), 7.37 (d, 2 H), 7.19 (t, 1 H), 6.92-7.01 (m 4 H), 6.74-6.77 (m, 1 H), 6.64-6.68 (m, 2 H), 5.80 (s, 2 H), 4.13 (q, 2 H), 3.88-3.98 (m, 4 H), 3.69 (s, 3 H), 1.34-1.45 (m, 4 H), 1.04 (t, 3 H), 0.56-0.66 (m, 2 H), 0.34-0.44 (m, 2 H).

Example 145

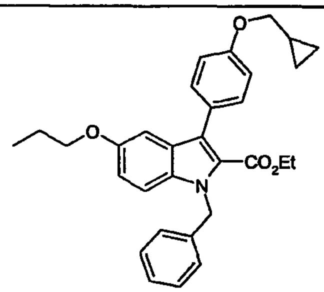
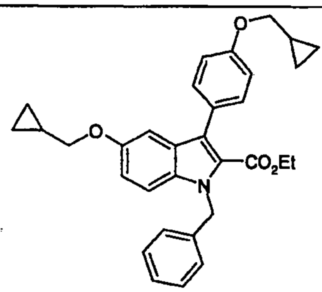
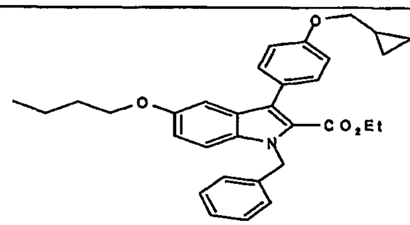
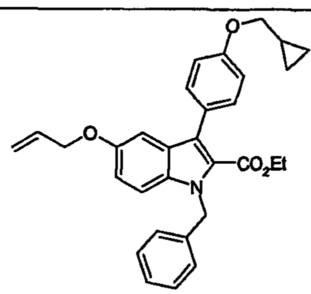
Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-5-(2-ethoxyethoxy)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate

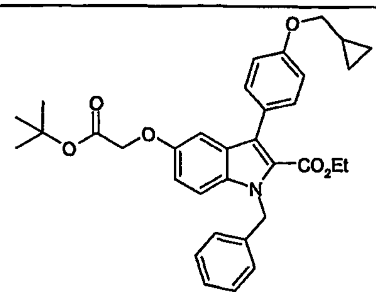
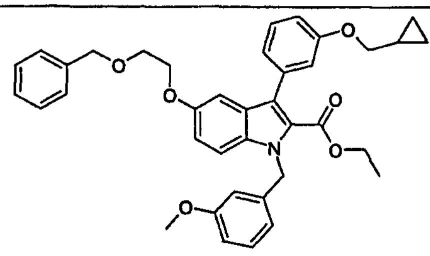
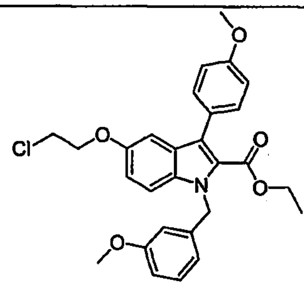
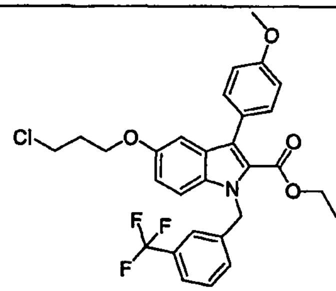
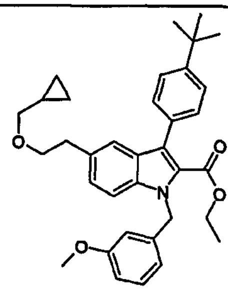


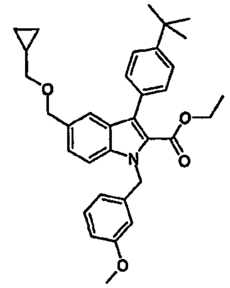
A solution of ethyl 3-[3-(cyclopropylmethoxy)phenyl]-5-(2-hydroxyethoxy)-1-(3-methoxybenzyl)-1-*H*-indole-2-carboxylate (Example **223**, 110 mg, 0.23 mmol) was added to a cooled (0 °C) and stirred suspension of sodium hydride (12 mg, 0.50 mmol) in *N,N*-dimethylformamide (5 mL). The cold bath was removed and the reaction was stirred for 1 h. Ethyl iodide (80 µL, 156 mg, 1.0 mmol) was added and the reaction was stirred for an additional hour. The reaction was quenched with methanol (1 mL) and then diluted with water (50 mL). The product was extracted with ethyl acetate (3x30 mL) and then the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 4:1 hexane/ethyl acetate gave 62 mg (50%) of product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.42 (d, 1 H), 7.29-7.36 (m, 2 H), 7.14 (dd, 1 H), 6.94-7.02 (m, 4 H), 6.63-6.79 (m, 3 H), 5.78 (s, 2 H), 3.99-4.12 (m, 4 H), 3.86 (d, 2 H), 3.64-3.71 (m, 5

H), 3.48 (q, 2 H), 1.24-1.34 (m, 1 H), 1.11 (t, 3 H), 0.98 (t, 3 H), 0.54-0.64 (m, 2 H), 0.32-0.42 (m, 2 H).

The following compounds were prepared according to the methods of Examples **144 - 145:**

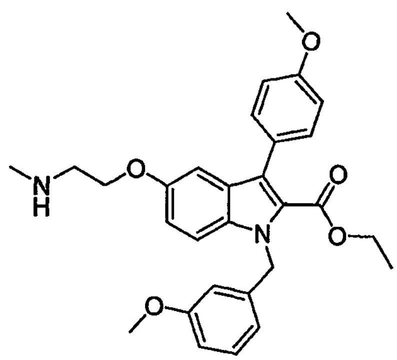
Ex. No.	Structure	Yield [%]	MS $[M+H^+]$	Rf	mp [°C]
146		53		0.85 (Hexane/ ethyl acetate 5:1)	
147		49		0.85 (Hexane/ ethyl acetate 5:1)	
148		57		0.85 (Hexane/ ethyl acetate 5:1)	
149		55		0.85 (Hexane/ ethyl acetate 5:1)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
150		80		0.85 (Hexane/ ethyl acetate 5:1)	
151		65			
152		80	494.1	0.27 (Hexane/ ethyl acetate 6:1)	
153		99	546.0	0.50 (Hexane/ ethyl acetate 2:1)	
154		38			

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
155		41	562.2		

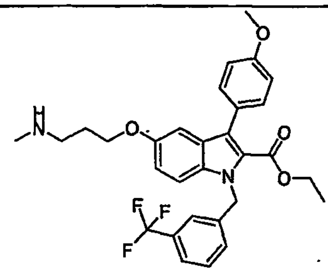
Example 156

Ethyl 1-(3-methoxybenzyl)-3-(4-methoxyphenyl)-5-[2-(methylamino)ethoxy]-1H-indole-2-carboxylate



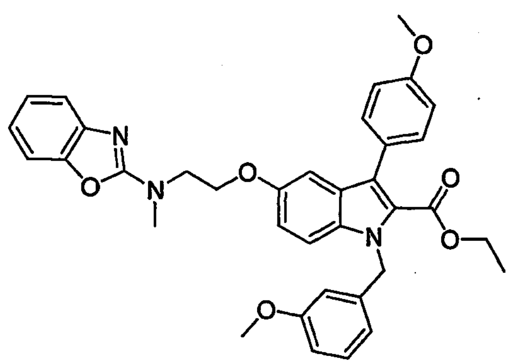
A reaction mixture of ethyl 5-(2-chloroethoxy)-1-(3-methoxybenzyl)-3-(4-methoxyphenyl)-1H-indole-2-carboxylate (Example **152**, 290mg, 0.588mmol) and methylamine in tetrahydrofuran (2 M, 40ml) was sealed in a stainless steel vessel (100ml, bomb) at 0°C. Then it was heated and stirred at 120°C for 3days in a oil bath. Oil bath was removed and the bomb was allowed to cooled to room temperature before opened. The reaction solution was transferred to an round-bottomed flask and solvent was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1N NaOH. The organic phase was dried over anhydrous sodium sulfate, concentrated and purified by flash column (silica gel, hexane: ethyl acetate =1:1 to ethyl acetate:2M NH3/ methanol =9:1). 214 mg desired product was obtained as a light yellow oil in 75%. MS (M+H) = 489.2, Rf = 0.28 (ethyl acetate : 2M NH3/methanol = 4:1).

The following compounds were prepared according to the method of Example **156**:

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
157		67	541.2	0.34 (ethyl acetate/ (2 M NH_3 in MeOH) 4:1	

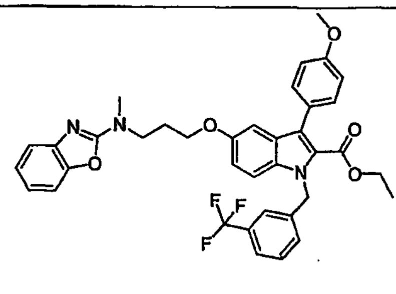
Example 158

Ethyl 5-{2-[1,3-benzoxazol-2-yl(methyl)amino]ethoxy}-1-(3-methoxybenzyl)-3-(4-methoxyphenyl)-1H-indole-2-carboxylate



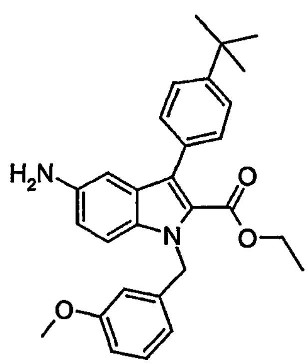
To a solution of Ethyl 1-(3-methoxybenzyl)-3-(4-methoxyphenyl)-5-[2-(methylamino)ethoxy]-1H-indole-2-carboxylate (Example **156**, 100 mg, 0.2028 mmol) in *N,N*-dimethylformamide (1.5ml) was added diisopropylethylamine (0.09ml, 0.5167mmol, 2.5eq.) and 2-chlorobenzoxazole (0.03ml, 0.2636mmol, 1.3eq.). The reaction mixture was heated at 120 °C for 4hr. After cooling the reaction was diluted with saturated aqueous sodium bicarbonate and then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na2SO4, concentrated *in vacuo* and purified by flash column (silica gel, dichloromethane to dichloromethane:methanol 95:5). The desired product was obtained as a light yellow oil in 97% yield (119mg), MS (M+H) = 606.3, Rf = 0.69 (dichloromethane/methanol 95:5).

The following compounds were prepared according to the method of Example **158**:

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
159		crude	658.3		

Example 160

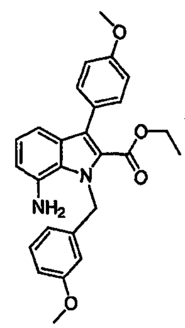
Ethyl 5-amino-3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Tin (II) chloride (8.5 g, 45 mmol) was added to a stirred solution of ethyl 3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-5-nitro-1*H*-indole-2-carboxylate (Example **28**, 4.5 g, 9.3 mmol) in EtOH (24 mL). The mixture was heated (50 °C) until there was a homogenous solution and then concentrated hydrochloric acid (16 mL) was added. The reaction was stirred at 60 °C for 2 h and then cooled. The pH of the solution was adjusted to pH=12 using 1 M aqueous sodium hydroxide and then the product was extracted with ethyl acetate (3x100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to leave 2.8 g (67%) of crude product that was taken to the next reaction without as proceeded to the next step without further purification. Mass spectroscopy gave MH^+ = 457.4 (exact mass calc'd for $C_{29}H_{32}N_2O_4$ = 456.24).

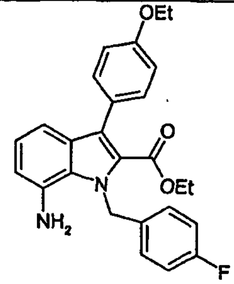
Example 161

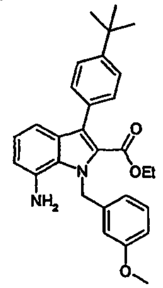
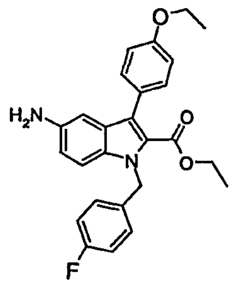
Ethyl 7-amino-3-(4-methoxyphenyl)-1-[(3-methoxyphenyl) methyl]indole-2-carboxylate



A solution of ethyl 3-(4-methoxyphenyl)-1-[(3-methoxyphenyl)methyl]-7-nitroindole-2-carboxylate (Example **96**, 425 mg, 0.99 mmol) in ethyl acetate (15 mL) was added to 10% Pd/C Degussa type (70 mg) and the resulting suspension put under a H_2 atmosphere and stirred for 18 h. The reaction was put back under argon, filtered through Celite, and the filtrate concentrated to a dark oil which was purified by flash chromatography on silica in 2:1 hexane:ethyl acetate to yield 401 mg, (100%) of an orange oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.28-7.22 (m, 2H), 7.19-7.12 (m, 1H), 7.00-6.95 (m, 2H), 6.89-6.83 (m, 1H), 6.80-6.70 M, 2H), 6.67-6.60 (m, 1H), 6.55-6.50 (m, 2H), 5.89 (s, 2H), 4.93 (s, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.63 (s, 3H), 0.94 (t, J = 7.1 Hz, 3H); Mass spectroscopy gave MH^+ = 431.2 (calc'd exact mass for $C_{26}H_{26}N_2O_4$ = 430.19); TLF R_f = 0.40 (2:1 hexane:ethyl acetate).

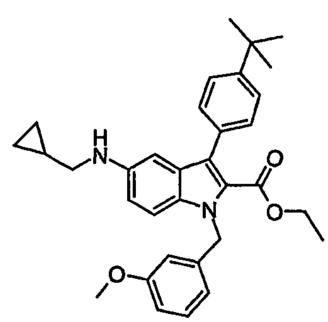
The following compounds were prepared according to the method of Example **161**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
162		84	433		

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
163		85	457		
164		63	433.4	0.34 (Hexane/ethyl acetate 2:1)	

Example 165

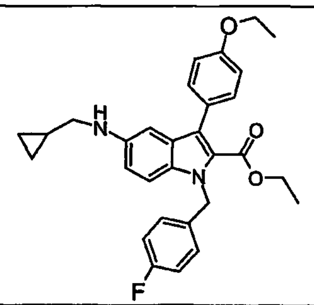
Ethyl 3-(4-*tert*-butylphenyl)-5-[(cyclopropylmethyl)amino]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Cyclopropanecarboxaldehyde (168 mg, 2.4 mmol) was added to a stirred mixture of ethyl 5-amino-3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example 160, 530 mg, 1.2 mmol) in toluene (12 mL) and molecular sieves (2 g). The reaction was stirred for 16 h and then filtered using toluene to rinse. The filtrate was concentrated *in vacuo* and the residue was dissolved in methanol (12 mL). Sodium borohydride (15 mg, 1.2 mmol) was added and the reaction was stirred for 2 h. The mixture was diluted with ethyl acetate (50 mL), washed with water and brine, dried over

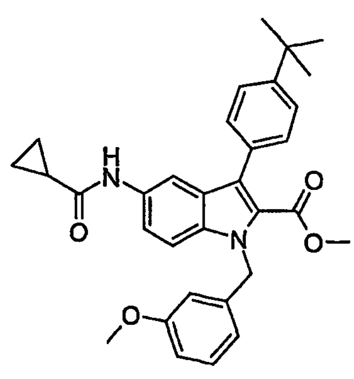
anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 4:1 hexane/ethyl acetate afforded 480 mg (78%) of desired product. The product had: ^{1}H NMR (300 MHz, acetone-D6) δ 7.45-7.48 (m, 2 H), 7.34-7.38 (m, 2 H), 7.31 (d, 1 H), 7.18 (dd, 1 H), 6.87 (dd, 1H), 6.77 (ddd, 1 H), 6.65-6.70 (m, 2 H), 6.62 (d, 1 H), 5.75 (s, 2 H), 4.68 (s, 1 H), 4.08 (q, 2 H), 3.69 (s, 3 H), 2.89 (d, 2 H), 1.37 (s, 9 H), 1.00-1.10 (m, 1 H), 0.93 (t, 3 H), 0.42-0.49 (m, 2 H), 0.16-0.25 (m, 2 H).

The following compounds were prepared according to the method of Example **165**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
166		72			

Example 167

Methyl 3-(4-*tert*-butylphenyl)-5-[(cyclopropylcarbonyl)amino]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



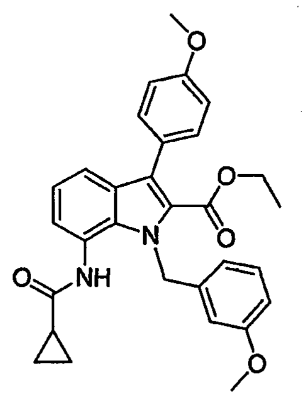
Triethylamine (0.12 mL, 91 mg, 0.90 mmol), dimethylaminopyridine (20 mg, 0.16 mmol), and cyclopropanecarbonyl chloride (82 μL, 94 mg, 0.90 mmol) were added successively to a cooled (0 °C) and stirred solution of methyl 5-amino-3-(4-*tert*-

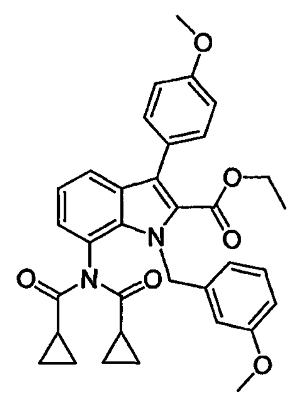
butylphenyl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **160**, 140 mg, 0.31 mmol) in dichloromethane (10 mL). The reaction was warmed to rt and stirred for 16 h. The solution was diluted with dichloromethane (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 4:1 hexane/ethyl acetate afforded 58 mg (37%) of desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 9.38 (s, 1 H), 8.02 (d, 1 H), 7.37-7.65 (m, 6 H), 7.19 (dd, 1 H), 6.80 (dd, 1 H), 6.66-6.74 (m, 2 H), 5.81 (s, 2 H), 3.73 (s, 3 H), 3.62 (s, 3 H), 1.70-1.80 (m, 1 H), 1.40 (s, 9 H), 0.82-0.90 (m, 2 H), 0.70-0.78 (m, 2 H).

Example 168 and 168A

Ethyl 7-(cyclopropylcarbonylamino)-3-(4-methoxyphenyl)-1-[(3-methoxyphenyl)-methyl]indole-2-carboxylate (Example 168) and

Ethyl 7-[cyclopropyl-N-(cyclopropylcarbonyl)carbonylamino]-3-(4-methoxyphenyl)-1-[(3-methoxyphenyl)methyl]indole-2-carboxylate (Example 168A)

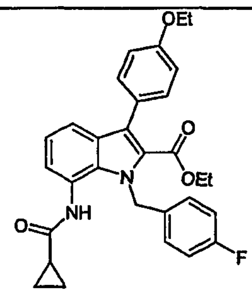
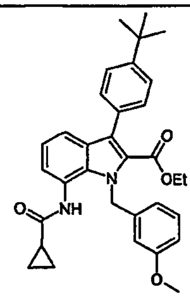
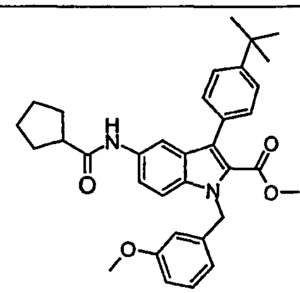




To a solution of ethyl 7-amino-3-(4-methoxyphenyl)-1-[(3-methoxyphenyl)-methyl]indole-2-carboxylate (Example **161**, 400 mg, 0.93 mmol) in tetrahydrofuran (5mL) was added triethylamine (0.278 mL, 2.00 mmol) and catalytic dimethylaminopyridine. The solution was stirred while cyclopropanecarbonyl chloride (0.10 mL, 1.1 mmol) was added. After 1 h stirring, the reaction was quenched with 1 M hydrogen chloride and the resulting mixture extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, adsorbed onto silica, and purified by flash chromatography on silica in a 3:1 to 1:1 hexane:ethyl acetate gradient to yield 170 mg (32%) of the diacylated Example **168A** and 190 mg (41%) of the monoacylated Example

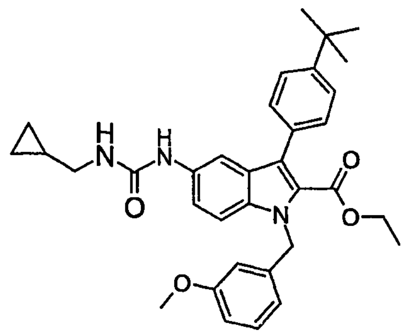
168: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 1H), 7.39-7.27 (m, 3H), 7.15-6.95 (m, 5H), 6.75-6.70 (m, 1H), 6.40-6.35 (m, 2H), 5.75 (s, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.62 (s, 3H), 1.80-1.70 (m, 1H), 0.94 (t, J = 7.1 Hz, 3H), 0.80-0.66 (m, 4H); TLC R_f = 0.06 (2:1 hexane:ethyl acetate (v/v)). Example **168A**: ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.58-7.53 (m, 1H), 7.40-7.34 (m, 2H), 7.24-7.11 (m, 3H), 7.07-7.02 (m, 2H), 6.80-6.73 (m, 1H), 6.42-6.33 (m, 2H), 5.63 (s, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 1.85-1.76 (m, 2H), 0.90 (t, J = 7.1 Hz, 3H), 0.84-0.60 (m, 8H); TLC R_f = 0.40 (2:1 hexane:ethyl acetate (v/v)).

The following compounds were prepared according to the methods of Examples **167 - 168**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
169		100	501		
170		39			
171		25			

Example 172

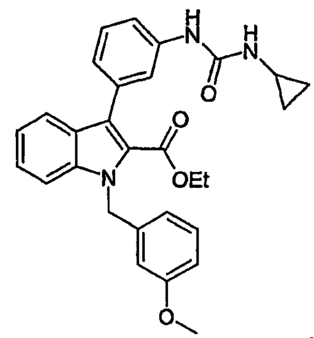
Ethyl 3-(4-*tert*-butylphenyl)-5-({[(cyclopropylmethyl)amino]carbonyl}amino)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Pyridine (0.18 mL, 174 mg, 2.2 mmol) and phosgene (1.9 M in toluene, 0.66 mL, 1.2 mmol) were added to a cooled (0 °C) and stirred solution of ethyl 5-amino-3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **160**, 500 mg, 1.1 mmol) in dichloromethane (10 mL). The reaction was warmed to rt and stirred for 3 h. The solution was concentrated *in vacuo* leaving crude Example **172**. A portion (260 mg, 0.54 mmol) of the intermediate was dissolved in dichloromethane (10 mL) and then (cyclopropylmethyl)amine (0.13 mL, 108 mg, 1.5 mmol) was added. The reaction was stirred at rt for 16 h and then diluted with dichloromethane (100 mL). The solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 3:1 hexane/ethyl acetate gave 160 mg (54%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 8.08 (d, 1 H), 7.09-7.45 (m, 7 H), 6.60-6.78 (m, 3 H), 6.33 (dd, 1 H), 5.76 (s, 2 H), 3.91 (q, 2 H), 3.68 (s, 3 H), 1.32 (s, 3 H), 0.87-0.96 (m, 1 H), 0.72 (t, 3 H), 0.31-0.41 (m, 2 H), 0.11-0.21 (m, 2 H).

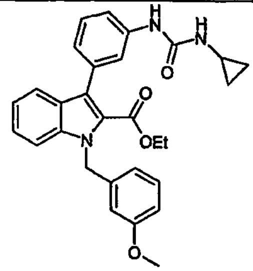
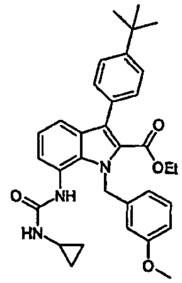
Example 173

Ethyl 3-{3-[(cyclopropylamino)carbonylamino]phenyl}-1-[(3-methoxyphenyl)methyl]indole-2-carboxylate



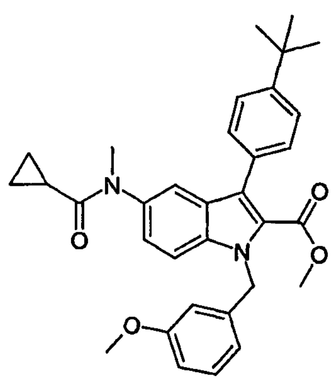
To a 25 mL round-bottomed flask at rt was charged with ethyl 3-(3-aminophenyl)-1-[(3-methoxyphenyl)methyl]indole-2-carboxylate (Example 93, 222 mg, 0.55 mmol) and dichloromethane (1.5 mL). The resulting solution was cooled to 0 °C, to which was added pyridine (0.09 mL, 1.1 mmol) and phosgene (20% in toluene, 0.35 mL, 0.66 mmol). The mixture was left stirred at 0 °C for 2 hours and rt for 2 hours before it was concentrated *in vacuo*. The residue was dissolved in dichloromethane (2 mL) and cyclopropylamine (0.11mL, 1.65 mmol) was added. The mixture was left at rt for 15 minutes before it was mixed with hydrochloric acid (1 N) and extracted with dichloromethane (10 mL). The organic layer was washed with aqueous sodium bicarbonate, brine, and dried over anhydrous magnesium sulfate. The crude mixture was purified with silica gel flash chromatography using hexane/ethyl acetate (3/1) as the eluant to give ethyl 3-{3-[(cyclopropylamino)carbonylamino]phenyl}-1-[(3-methoxyphenyl)methyl]indole-2-carboxylate (140 mg, 53%): MS (electrospray, MH^+) calcd for $C_{29}H_{30}N_3O_4$ 484.2, found 484.1; ^{1}H NMR (DMSO-d^6) δ 8.36 (s, 1H), 7.52-7.64 (m, 3H), 7.15-7.38 (m, 5H), 6.95 (ddd, J = 6.9 Hz, 1H), 6.79 (dd, J = 8.1, 1.9 Hz, 1H), 6.65 (dd, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.38 (d, J = 2.6 Hz, 1H), 5.77 (s, 2H), 4.10 (q, J = 7.1 Hz), 3.68 (s, 3H), 2.50-2.60 (m, 1H), 0.97 (t, J = 7.1 Hz), 0.60-0.64 (m, 2H), 0.39-0.41 (m. 2H).

The following compounds were prepared according to the methods of Examples **172 - 173:**

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
174		53	484.1		
175		21			

Example 176

Methyl 3-(4-*tert*-butylphenyl)-5-[(cyclopropylcarbonyl)(methyl)amino]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate

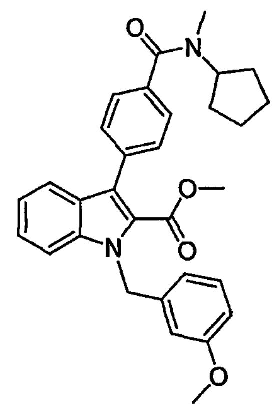


Sodium hydride (192 mg, 0.800 mmol) was added to a cooled (0 °C) and stirred solution of 3-(4-tert-butylphenyl)-5-[(cyclopropylcarbonyl)amino]-1-(3-methoxybenzyl)-1H-indole-2-carboxylic acid (Example **167**, 94.5 mg, 0.190 mmol) in tetrahydrofuran (5 mL). The cold bath was removed and stirring was continued for 1 h. Dimethylsulfate (0.75 mL, 101 mg, 0.80 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with water (50 mL) and then extracted with ethyl acetate

(3x30 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 40% ethyl acetate/hexane afforded 894 mg (90%) of the desired product. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.50 (m, 3 H), 7.28-7.36 (m, 3 H), 7.11-7.24 (m, 2 H), 6.59-6.76 (m, 3 H), 5.70 (s, 2 H), 3.90 (s, 3 H), 3.69 (s, 3 H), 3.21 (s, 3 H), 1.34 (s, 9 H), 1.15-1.35 (m, 1 H), 0.87-0.97 (m, 2 H), 0.48-0.58 (m, 2 H); mass spectroscopy gave MH^+ = 525.3 (calc'd exact mass for $C_{33}H_{36}N_2O_4$ = 524.27).

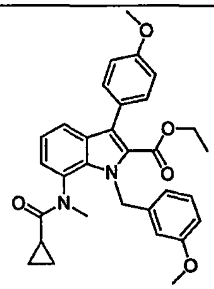
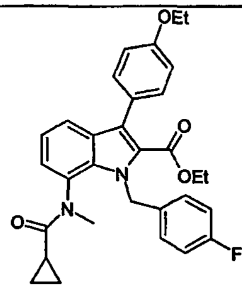
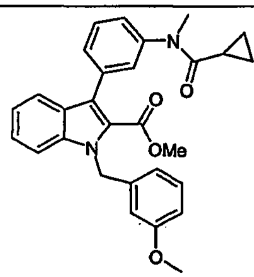
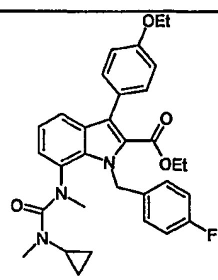
Example 177

Methyl 3-[4-(N-cyclopentyl-N-methylcarbamoyl)phenyl]-1-[(3-methoxyphenyl)methyl]indole-2-carboxylate



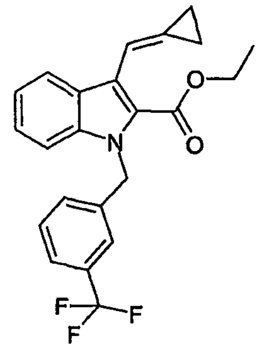
To a solution of 3-[4-(N-cyclopentylcarbamoyl)phenyl]-1-[(3-methoxyphenyl)-methyl]indole-2-carboxylic acid (Example 96, 260 mg, 0.53 mmol) in tetrahydrofuran (5 mL), was added a 1.0 M solution of potassium *tert*-butoxide in tetrahydrofuran (0.70 mL, 0.70 mmol) and the resulting orange solution was stirred for 5 minutes. Iodomethane (0.10 mL, 1.6 mmol) was added and the reaction was allowed to stir at RT for 18 h. The reaction was quenched with 10% aqueous citric acid and the resulting mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, adsorbed onto silica, and purified by flash chromatography on silica in 2:1 hexane:ethyl acetate to yield 113 mg (43%) of a clear oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67-7.67 (m, 1H), 7.59-7.53 (m, 1H), 7.51-7.40 (m, 4H), 7.40-7.33 (m, 1H), 7.22-7.14 (m, 2H), 6.82-6.776 (m, 1H), 6.67-6.64 (m, 1H), 6.62-6.57 (m, 1H), 5.78 (s, 2H), 3.67 (s, 3H), 3.61 (s, 3H), 2.86 (s, 3H), 1.83-1.32 (m, 9H); mass spectroscopy gave MH^+ = 511.3 (calc'd exact mass for $C_{32}H_{34}N_2O_4$ = 510.25); TLF R_f = 0.40 (1:1 hexane:ethyl acetate).

The following compounds were prepared according to the method of Example 177:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
178		crude	513.2	0.28 (Hexane/ethyl acetate 2:1)	
179		87			
180		89	469		
181		87			

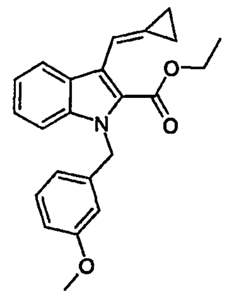
Example 182

Ethyl 3-(cyclopropylidenemethyl)-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate



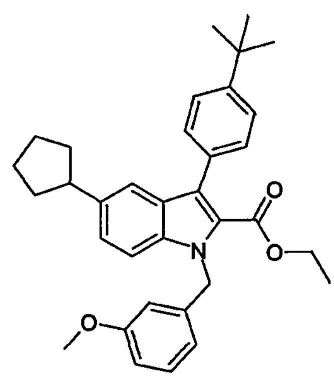
Sodium hydride (60% dispersion in mineral oil, 128 mg, 3.20 mmol) was suspended in anhydrous tetrahydrofuran (10 mL) and cooled to 0 °C. Triphenyl-cyclopropylphosphonium bromide (1.23 g, 3.20 mmol) was added as a solid all at once, and the mixture was allowed to stir at room temperature. Once gas evolution ceased, a tetrahydrofuran solution of ethyl 3-formyl-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate (Example **40**, 1.0 g, 2.7 mmol) was added, the mixture was stirred for 15 hours, and the resulting mixture was partitioned between water and ethyl acetate. Layers were separated, and the aqueous layer was extracted with ethyl acetate (2x). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. The resulting crude oil was purified by flash chromatography on silica gel eluted with 5% ethyl acetate/hexane. The title compound was collected as a bright yellow oil (403 mg, 38%). The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 1 H), 7.53 (s, 1 H), 7.41-7.38 (m, 2 H), 7.29-7.20 (m, 3 H), 7.15-7.12 (m, 1 H), 7.05 (d, 1 H), 5.72 (s, 2 H), 4.27 (q, 2 H), 1.50-1.45 (m, 2 H), 1.25 (t, 3 H), 0.83-0.76 (m, 2 H); mass spectroscopy gave MH^+ = 400.2 (calc'd exact mass for $C_{23}H_{20}F_3NO_2$ = 399.14).

The following compounds were prepared according to the method of Example **182**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
183		43	362		

Example 184

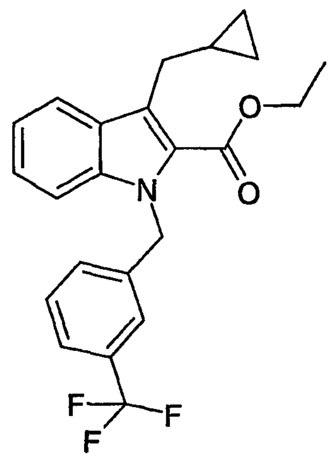
Ethyl 3-(4-*tert*-butylphenyl)-5-cyclopentyl-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



A solution of ethyl 5-(1-cyclopenten-2-yl)-3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **128**, 225 mg, 0.44 mmol) in ethyl acetate (3 mL) and EtOH (3 mL) was added to a slurry of 10% palladium on charcoal (100 mg) in ethyl acetate (2 mL) and EtOH (2 mL). The reaction was placed under hydrogen (1 atm) and stirred for 16 h. The mixture was filtered through a pad of Celite using ethyl acetate to rinse. Evaporation of the filtrate gave 210 mg (93%) of the product. The product had: ^{1}H NMR (300 MHz, acetone-D$_6$) δ 7.37-7.53 (m, 6 H), 7.28 (dd, 1 H), 7.19 (dd, 1 H), 6.67-6.82 (m, 3 H), 5.83 (s, 3 H), 4.08 (q, 2 H), 3.75 (s, 3 H), 3.06 (p, 1 H), 1.99-2.06 (m, 2 H), 1.47-1.83 (m, 6 H), 1.40 (s, 9 H), 0.98 (t, 3 H).

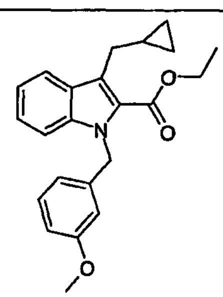
Example 185

Ethyl 3-(cyclopropylmethyl)-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate



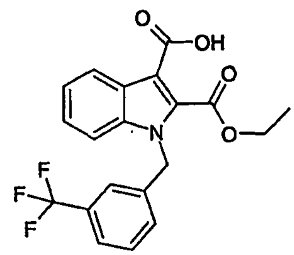
Ethyl 3-(cyclopropylidenemethyl)-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate (Example **182**, 140 mg, 0.351 mmol) was stirred over Lindlar catalyst (28 mg) in ethanol (15 mL) under 1 atmosphere of hydrogen for 1 hour. The mixture was filtered through Celite with an excess of ethanol. The filtrate was concentrated, and the resulting crude oil was purified by flash chromatography on silica gel eluted with 20% Et_2O/hexane. The title compound was collected as a yellow oil (95 mg, 67%). The product had: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.78 (d, 1 H), 7.56-7.45 (m, 4 H), 7.34-7.32 (m, 1 H), 7.28-7.26 (m, 1 H), 7.16-7.13 (m, 1 H), 5.93 (s, 2 H), 4.32 (q, 2 H), 3.08 (d, 2 H), 1.31 (t, 3 H), 1.13-1.15 (m, 1 H), 0.42-0.38 (m, 2 H), 0.29-0.26 (m, 2 H).

The following compounds were prepared according to the methods of Examples **184 - 185**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
186		55			

Example 187

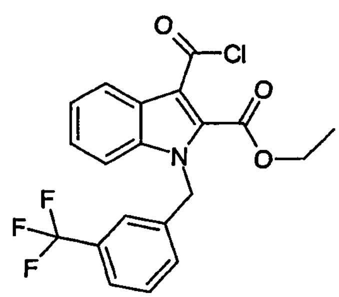
Ethyl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate-3-carboxylate



To a solution of ethyl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate-3-carboxaldehyde (Example **40**, 6.0g, 15.9 mmol) in pH 3.5 phosphate buffer (48 mL) and t-butanol (90 mL) was added 2-methyl-2-butene (30 mL) and sodium chlorate (2.1 g, 1.5 eq.). The reaction was stirred at room temperature for 16 hours and then extracted with dichloromethane (3x200 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica afforded the desired product as a white solid. The product had: ^{1}H NMR (300 MHz, dmso-D_6) 8.03 (d, 1 H), 7.5 – 7.65 (m, 4 H), 7.2-7.39 (m, 3 H), 5.61 (s, 2 H), 4.26 (q, 2 H), 1.15 (t, 3 H).

Example 189

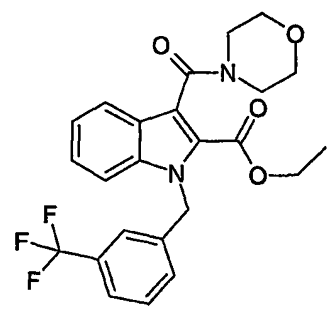
Ethyl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate-3-carbonyl chloride



Ethyl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate-3-carboxylic acid (Example **187**, 100 mg, 0.25 mmol) was taken up in dichloromethane (10 mL) with a catalytic amount of DMF, and the mixture was cooled (0 °C.) Oxalyl chloride (0.044 mL, 2 eq.) was added, and the reaction was stirred for 1 hour. The mixture was concentrated *in vacuo* and used directly with no further purification.

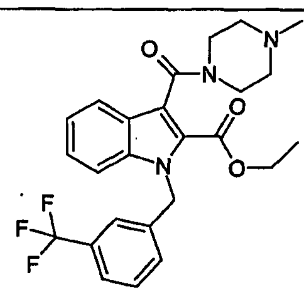
Example 191

Ethyl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate -3-carboxylic acid, morpho-line amide



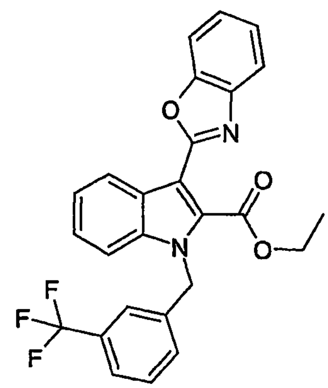
Ethyl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate-3-carbonyl chloride (Example **189**, 0.16 g, 0.4 mmol) was taken up in excess morpholine (0.3 mL) at room temperature. The reaction was stirred for 72 hours, quenched with water, and extracted with diethyl ether (2 x 25 mL.) The combined organic extracts were dried over sodium sulfate and purified by flash chromatography to yield 0.268 mg (91%) of the desired product. The product had: ^{1}H NMR (300 MHz, dmso-D_6) δ 7.42 – 7.75 (m, 5 H), 7.4 (t, 1 H), 7.22 (m, 2 H), 5.95 (s, 2 H), 4.21 (q, 2 H), 3.0-3.8 (broad m, 8 H), 1.1 (t, 3 H)

The following compounds were prepared according to the method of Example **191:**

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
192		86			

Example 193

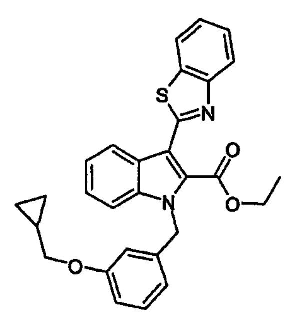
Ethyl-3-benzoxazol-2-yl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate



Ethyl-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate-3-carbonyl chloride (Example **189**) was prepared as above from the corresponding acid (600 mg, 1.53 mmol.) The crude material was taken up in dichloromethane (50 mL) and cooled to 0 °C. Triethylamine (0.85 mL, 4 eq.) was added, followed by 2-aminophenol (0.5 g, 3 eq.), and the reaction mixture was allowed to warm to room temperature. The mixture was quenched with 1 N HCl, and the organic layers were separated and concentrated *in vacuo*. The crude intermediate was taken up in toluene (20 mL) with p-toluenesulfonic acid (0.73 g) and heated to reflux for 3 hours. The reaction was cooled to room temperature, quenched with water, and extracted with ethyl acetate (3 x 75 mL.) The organic layers were dried over sodium sulfate and purified by flash chromatography over silica gel to give the desired product (260 mg, 37 %.) The product had: ^{1}H NMR (300 MHz, dmso-D_6) δ 8.3 (d, 1 H), 7.35-7.9 (m, 11 H), 5.81 (s, 2 H), 4.37 (q, 2 H), 1.16 (t, 3 H) Mass spectroscopy gave $MH^+ = 437.2$ (calc'd exact mass for $C_{24}H_{15}F_3N_2O_3 = 436.1$).

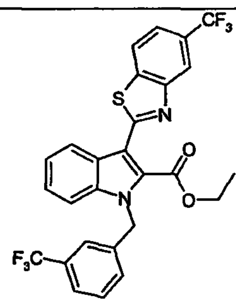
Example 194

Ethyl-3-benzthiazol-2-yl-1-(3-cyclopropylmethoxybenzyl)-1H-indole-2-carboxylate



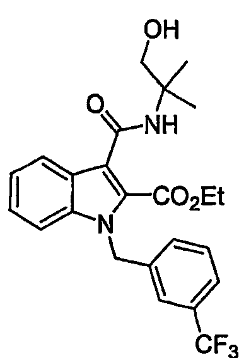
Ethyl-3-benzthiazol-2-yl-1-(3-cyclopropylmethoxybenzyl)-1H-indole-2-carboxaldehyde (Example **41**, 0.42 g, 1.1 mmol) was taken up in EtOH (30 mL) at room temperature. 2-aminothiophenol (0.15 g, 1.05 eq.) was added, followed by conc. HCl (0.5 mL), and the reaction mixture was heated to reflux for 24 hours. The mixture was cooled to room temperature, quenched with water and extracted with diethyl ether (3 x 50 mL.) The organic layers were separated, dried over sodium sulfate, and concentrated *in vacuo* to give the desired product (0.38 g, 71 %) which was taken to the hydrolysis step without further purification.

The following compounds were prepared according to the method of Example **194**:

Ex. No.	Structure	Yield [%]	MS $[M+H^+]$	Rf	mp [°C]
195		crude			

Example 196

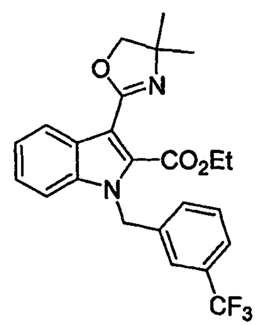
Ethyl 3-{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate



To a 0°C solution of Example **189** (545 mg, 1.28 mmol) in dichloromethane (8 mL) was added 2-hydroxy-1,1-dimethyl-ethylamine (285 mg, 3.2 mmol). Triethyl amine (0.7 mL, 5.12 mmol) was added in one portion. The mixture was stirred for 15 min. and then allowed to warm to r.t. over 20 min. The reaction was quenched with 1N HCl and the resulting mixture was washed with 1N HCl (2X). The organic layer was dried over anhydrous sodium sulfate, concentrated, and filtered through a short plug of silica gel (elution with 8:92 methanol:dichloromethane). Concentration of the filtrate provide 440 mg (74 %) of Example **196**. LRMS (+esi) obs'd: 463.1; calc'd 462.2.

Example 197

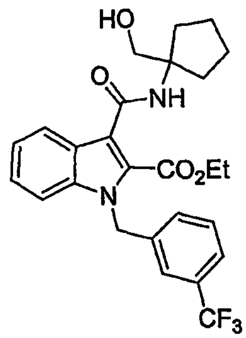
Ethyl 3-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-[3-(trifluoromethyl)benzyl)-1H-indole-2-carboxylate



A solution of Example **196** (440 mg, 0.95 mmol) and *p*-toluenesulfonic acid monohydrate (170 mg, 0.89 mmol) in toluene (6 mL) was refluxed for 1.5 h. The mixture was cooled and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated. The remaining material was purified by flash chromatography (silica gel, 10:90 methanol:dichloromethane) to provide 100 mg (24%) of Example **197**, which was used in the next step without purification. Rf = 0.95 (1/9 methanol/dichloromethane); LRMS (+esi) obs'd: 445.2; calc'd 444.2.

Example 198

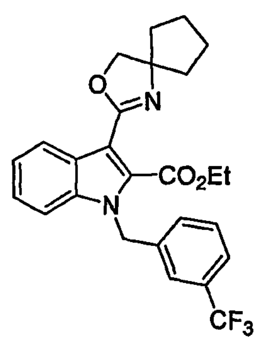
Ethyl 3-({[1-hydroxymethyl)cyclopentyl]amino}carbonyl)-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate



To a 0°C solution of acid chloride Example **189** (434 mg, 1.02 mmol) in dichloromethane (7 mL) was added cycloleucinol (295 mg, 2.55 mmol). Triethyl amine (0.57 mL, 4.08 mmol) was added in one portion. The mixture was stirred for 1h and was then allowed to warm to r.t. over 40 min. The reaction was diluted with water and the organic layer was washed with 1N HCl, dried over anhydrous sodium sulfate and concentrated to afford 498 mg of Example **198** which was used without further purification. LRMS (+esi) obs'd: 489.1; calc'd 488.2.

Example 199

Ethyl 3-(3-oxa-1-azaspiro[4.4]non-1-en-2-yl)-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate

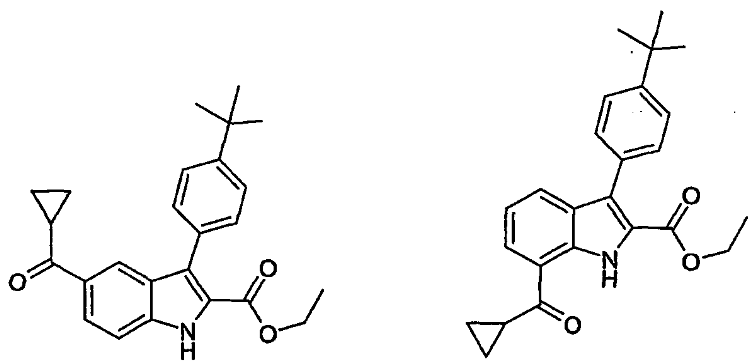


A solution of Example **198** (498 mg, 1.02 mmol) and *p*-toluenesulfonic acid monohydrate (210 mg, 1.1 mmol) in toluene (7 mL) was refluxed for 2 h. The mixture was cooled and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash chromatography (5:95 methanol:dichloromethane)

provided impure Example **199**. Rf = 0.96 (6/94 methanol/dichloromethane); LRMS (+esi) obs'd: 471.2; calc'd 470.2.

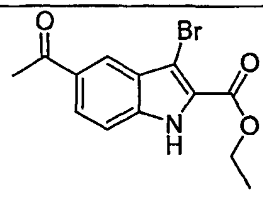
Example 200 and 201

Ethyl 3-(4-t-butylphenyl)-5-(cyclopropyl)carbonyl-1H-indole-2-carboxylate (Example 200) and Ethyl 3-(4-t-butylphenyl)-7-(cyclopropyl)carbonyl-1H-indole-2-carboxylate (Example 201)



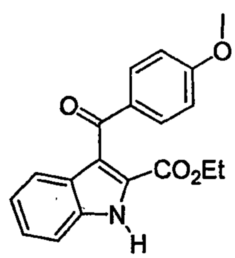
Aluminum chloride (4.07 g, 1.5 eq.) was suspended in dichloromethane (70 mL) and cooled to 0 °C. Cyclopropyl carbonyl chloride (3.2 g, 1.5 eq.) was added slowly, and the mixture was stirred for 15 minutes. A solution of ethyl 3-(4-t-butylphenyl)-1H-indole-2-carboxylate (Example **224**, 5.16 g, 20.4 mmol) in dichloromethane (20 mL) was added dropwise. The reaction was allowed to warm to room temperature, and was then heated to reflux for 24 hours, cooled to room temperature, quenched with water and diluted with diethyl ether. The organic layers were washed with water and 1N HCl and dried over sodium sulfate, then purified by flash chromatography over silica to give 5.25 g of the 5-acylated Example **200**, which had ^{1}H NMR (300 MHz, $CDCl_3$) 9.35 (bs, 1H), 8.4 (s, 1 H), 8.03 (d, 1 H), 7.45 (m, 5 H), 4.35 (q, 2 H), 2.72 (m, 1 H), 1.4 (s, 9 H), 0.9-1.4 (m, 9 H) and 1.27 g of the 7-acylated Example **201**, which had: ^{1}H NMR (300 MHz, $CDCl_3$) 10.9 (bs, 1H), 8.17 (d, 1 H), 7.92 (d, 1 H), 7.45 (m, 5 H), 4.35 (q, 2 H), 2.86 (m, 1 H), 1.4 (s, 9 H), 1.1-1.4 (m, 9 H) .

The following compounds were prepared according to the method of Example **200**:

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
202		25		0.25 (Hexane/ethyl acetate 4:1)	

Example 203

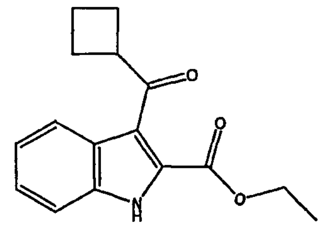
Ethyl 3-(4-methyoxybenzoyl)-1H-indole-2-carboxylate (53354-02)



A 0°C suspension/solution of $AlCl_3$ (693 mg, 5.2 mmol) and 4-methoxybenzyl acid chloride (887 mg, 5.2 mmol) in 1,2 dichloroethane (10 mL) was stirred for 5 min. A solution of indole (0.5 gm, 2.6 mmol) in 1,2-dichloroethane (10 mL) was added dropwise and upon complete addition the mixture was warmed to reflux for 1h. The mixture was cooled and poured over ice. The aq. layer was extracted with ethyl acetate. The extracts were washed with sat. aq. Na_2CO_3, dried and concentrated. Purification of the remaining oil by flash chromatography (silica gel, elution with 5:5 ethyl acetate:hexane) afforded 481 mg (57%) of Example **203**. Rf = 0.48 (1/1 hexane/ethyl acetate); LRMS (+esi) obs'd: 324.1; calc'd 323.1.

Example 204

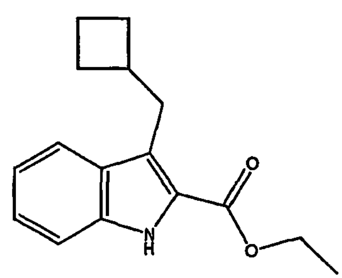
Ethyl 3-(cyclobutylcarbonyl)indole-2-carboxylate



To a 50 mL reaction vial and stir bar was charged with 0.563 g of $FeCl_3$ (5.28 mmoles) followed by addition of 10 ml of dichloromethane. The heterogeneous solution was cooled to 0°C followed by addition of a 10 mL dichloromethane solution of ethyl indole-2-carboxylate (0.5 g, 2.64 mmoles). The contents were maintained at 0 c for 0.5 hours then poured into 30 mL of ice water and neutralized with $NaHCO_3$ saturated solution. The contents were then extracted with 3 x 20 mL of dichloromethane and dried over Na_2SO_4 and concentrated *in vacuo* to yield 0.71 g (99.0 %) of a white solid (Rf- 0.10 in 10% ethyl acetate/hexane). The product had: ^1H NMR (300 MHz, acetone-D_6); δ 11.4 Hz (s, 1H), 7.93 Hz (dd, 1H), 7.54 Hz (dt, 1H), 7.34 Hz (td, 1H), 7.20 Hz (td, 1H), 4.43 Hz (q, 2H), 2.32 Hz (m, 1H), 2.17 Hz (m, 4H), 1.97 Hz (m, 2H), 1.40 Hz (t, 3H); mass spectroscopy gave M^+ of 272.2 (calc'd mass for $C_{16}H_{17}NO_3$ of 271.31).

Example 205

Ethyl 3-(cyclobutylmethyl)indole-2-carboxylate

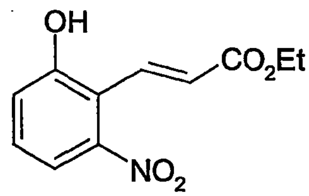


To a dry 50 mL round bottom flask and stir bar was charged with ethyl-3-(cyclobutylcarbonyl)indole-2-carboxylate (Example **204**, 0.81g, 3.0 mmol) followed by addition of TFA (5.6 mL). The contents were stirred and cooled to 0°C followed by dropwise addition of triethylsilane (1.56 mL, 9.8 mmol) via syringe. The contents of the reaction were maintained at 0°C for 20 minutes then heated to reflux for 3 hours. The

reaction was cooled to room temperature followed by addition of water (20 mL) triturating a solid. The solid was filtered and washed 3 x 20 mL of water and air dried providing 0.76 g (99.0 % yield) of a white solid. The product had a Rf of 0.38 10% ethyl acetate/hexane; ^{1}H NMR (300 MHz, acetone-D$_6$); 10.5 Hz (s, 1H), 7.71 Hz (dd, 1H), 7.46 Hz (dt, 1H) 7.26 Hz (td, 1H), 7.08 Hz (td, 1H) 4.37 Hz (q, 2H), 3.24 Hz (d, 2H), 2.74 Hz (m, 1H), 1.93 Hz (m, 2H), 1.80 Hz (m, 4H), 1.39 Hz (t, 3H) mass spectroscopy gave M$^-$ of 256.5 (calc'd mass for $C_{16}H_{19}NO_2$ of 257.33).

Example 206

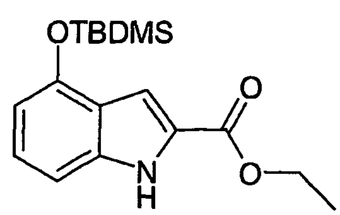
Ethyl (2E)-3-(2-hydroxy-6-nitrophenyl)prop-2-enoate



To a thick-walled vessel was charged with 2-bromo-3-nitrophenol (1.16 g, 5.32 mmol), ethyl acrylate (666 mg, 0.72 mmol), tri-(*o*-tolyl)phosphine (65 mg, 0.21 mmol), palladium acetate (12 mg, 0.05 mmol), and triethylamine(10 mL). The vessel was then sealed and the resulting mixture was heated to 100 °C overnight. In the morning, the vessel was cooled to rt and the mixture was poured into water. The mixture was acidified with hydrochloric acid and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The residue was purified with silica gel flash chromatography by using hexane/ethyl acetate (2/1) as the eluant to give ethyl (2E)-3-(2-hydroxy-6-nitrophenyl)prop-2-enoate (883 mg, 70%): R_f 0.16 (3/1 hexane/ethyl acetate); ^{1}H NMR (CDCl$_3$) δ 7.6(d, J = 16.1 Hz, 1H), 7.05-7.23 (m, 3H), 6.71 (dd, J = 16.1, 0.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 2H).

Example 207

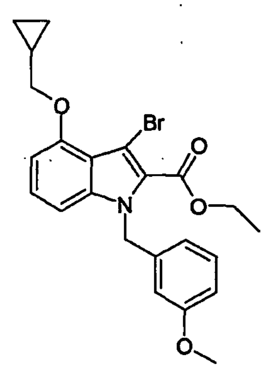
Ethyl 4-(1,1,2,2-tetramethyl-1-silapropoxy)indole-2-carboxylate



To a round-bottomed flask at rt was charged with ethyl (2E)-3-(2-hydroxy-6-nitrophenyl)prop-2-enoate (Example **206**, 260 mg, 1.10 mmol), *N,N*-dimethylformamide (2 mL), *t*-butyldimethylsilyl chloride (198 mg, 1.32 mmol), and imidazole (150 mg, 2.20 mmol). The resulting mixture was left stirring at rt for 2 hours before hydrochloric acid was added and the mixture was extracted with diethyl ether (2 x 20 mL). The combined organic layer was washed with water, brine, and dried over anhydrous sodium sulfate. The concentrated residue was used without further purification. It was mixed with triethyl phosphite (920 mg, 5.50 mmol) and heated to 170 °C for 3 hours before it was cooled to rt and diluted with ethyl acetate. The mixture was washed with water, brine and dried over anhydrous sodium sulfate. The concentrated residue was purified with silica gel flash chromatography by using hexane/ethyl acetate (3/1) as the eluant to give ethyl 4-(1,1,2,2-tetramethyl-1-silapropoxy)indole-2-carboxylate as a white solid (224 mg, 64%): R_f 0.57 (3/1 hexane/ethyl acetate); %): MS (MH^+) calcd for $C_{17}H_{26}NO_3Si$ 320.2, found 320.2; ^1H NMR (DMSO-d_6) δ 11.87 (br s, 1H), 6.99-7.15 (m, 3H), 6.47 (dd, J = 7.3, 0.6 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H), 1.01 (s, 9H), 0.22 (s, 6H).

Example 208

Ethyl 3-bromo-4-(cyclopropylmethoxy)-1-[(3-methoxyphenyl)methyl]indole-2-carboxylate

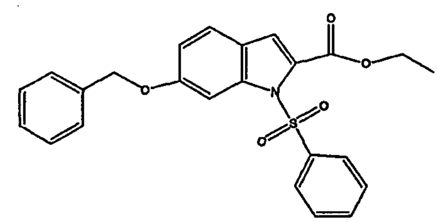


To a round-bottomed flask at rt was charged with ethyl 4-(1,1,2,2-tetramethyl-1-silapropoxy)indole-2-carboxylate (Example **18**, 100 mg, 0.19 mmol), tetrabutyl-ammonium fluoride (1M in tetrahydrofuran, 0.29 mL, 0.29 mmol), molecule sieves (3A, 30 mg), and tetrahydrofuran (1 mL). After 0.5 hours at rt, cyclopropylmethyl bromide (52 mg, 0.04 mL, 0.38 mol) was added to the reaction mixture. After 2 hours at rt, the mixture was diluted with water and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The concentrated residue was purified with silica gel flash chromatography by using

hexane/ethyl acetate (3/1) as the eluant to give ethyl 3-bromo-4-(cyclopropylmethoxy)-1-[(3-methoxyphenyl)methyl]indole-2-carboxylate (90 mg, 100%). The product was used without further purification: MS (MH^+) calcd for $C_{23}H_{25}BrNO_4$ 458.1, found 458.5; ^{1}H NMR (DMSO-d_6) δ 7.17-7.30 (m, 3H), 6.82 (dd, J= 8.2, 1.7 Hz, 1H), 6.66 (d, J =6.9 Hz, 1H), 6.59-6.61 (m, 1H), 6.51 (d, J = 7.6 Hz, 1H), 5.72 (s, 2H), 4.33 (q, J = 7.0 Hz, 2H), 4.02 (d, J = 6.4 Hz, 2H), 3.71 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), 0.85-0.95 (m, 1H), 0.59-0.66 (m, 2H), 0.45-0.50 (m, 2H).

Example 209

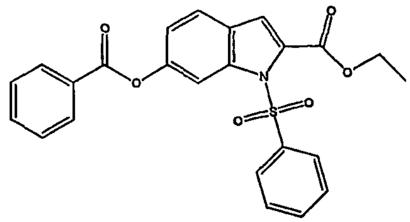
Ethyl 6-(benzyloxy)-1-(phenylsulfonyl)indole-2-carboxylate



To a dry 100 ml round bottom flask and stir bar attached with a septa and purged with argon was charged with 7.5 mL of tetrahydrofuran and 0.33g (3.25 mmol) of diisopropylamine then cooled to –78°C. To the cooled solution of the amine n-BuLi (2.6M hexane, 1.20 mL, 3.1 mmol) was added dropwise via syringe and allowed to stir for 20 minutes at –78°C. At this time a 7.5 mL tetrahydrofuran solution of 6-(phenylmethoxy)-1-(phenylsulfonyl)indole (Example 57, 1.06g, 2.95 mmol) was added to the LDA solution via cannula over a 10-15 minute period. The yellow solution was maintained at –78°C for 1 hour then warmed to 0°C for ½ hour followed by cooling to –78°C. Once cooled to –78°C 0.96g of ethyl chloroformate (8.85mmol) was rapidly added via syringe. Upon complete addition the contents were warmed to room temperature and stirred for ½ hour then quenched with 20 mL of water then extracted with 3x20mL of ethyl acetate. The organics were dried over Na_2SO_4 then concentrated *in vacuo*. The crude material was purified via SiO_2 column chromatography to yield 0.85g (67% yield) of a white solid. The product had a Rf of 0.15 10% ethyl acetate/hexane; ^{1}H NMR (300 MHz, Acetone-D_6); 7.90 Hz, (d, 2H), 7.66 Hz, (m, 2H), 7.54 Hz, (m, 4H), 7.40 Hz, (m, 2H), 7.21 Hz, (s, 1H), 7.03 Hz, (dd, 1H), 5.27 Hz, (s, 2H), 4.32 Hz, (q, 2H), 1.32 Hz, (t, 3H).

Example 210

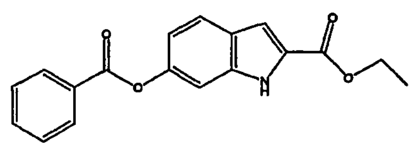
Ethyl 6-(benzoyloxy)-1-(phenylsulfonyl)indole carboxylate (dpd-53586-97)



To a dry 100 mL round-bottom flask, stir bar and purged with argon was charged with 5.10g of ethyl 6-hydroxy-1-(phenylsulfonyl)indole-2-carboxylate (Example 123, 15 mmol) followed by addition of 30 mL of anhydrous tetrahydrofuran and cooled to 0°C . To the rapidly stirring solution was added via syringe 15.2g of triethylamine (150 mmol) followed by slow addition of 3.15g of benzoyl chloride (22.4 mmol) via syringe while maintaining the solution at 0°C. The reaction was warmed to rt and stirred for an additional hour. The reaction was then quenched with 15mL of 3N HCl then extracted with 3x50 mL of ethyl acetate and dried over Na_2SO_4 then concentrated *in vacuo*. The crude material was purified via column chromatography to yield 4.7g (70.1% yield) of a white solid. The product had a Rf of 0.33 20% ethyl acetate/hexane; ^{1}H NMR (300 MHz, Acetone-D_6); 8.22 Hz, (d, 2H), 8.11 Hz, (m, 3H), 7.73 Hz, (m, 3H), 7.62 Hz, (t, 4H), 7.34 Hz, (s, 1H), 7.29 Hz, (dd, 1H).

Example 211

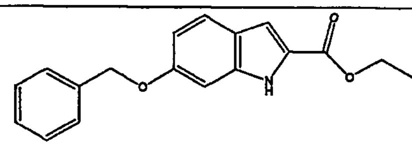
Ethyl 6-(benzoyloxy)indole-2-carboxylate



To a dry 100 mL and stir bar was charged with 4.70 g ethyl 6-(benzoyloxy)-1-(phenylsulfonyl)indole carboxylate (Example 210) and dissolved in 12.5 mL of anhydrous tetrahydrofuran then cooled to 0°C. To this rapidly stirring solution was added 35.0 mL 1.0 M tetrahydrofuran solution of potassium tert-butoxide dropwise via syringe. Upon complete addition the contents were warmed to room temperature and stirred an additional ½ hour then quenched with 10 mL of 3N HCl solution followed by addition of 30 mL of water. The reaction was extracted with 3x50 mL of ethyl acetate then dried over Na_2SO_4

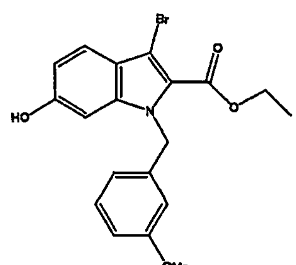
and concentrated *in vacuo*. The crude material was purified via column chromatography to yield 3.28g (99.0% yield) of an off white solid. The product had a Rf of 0.42 20% ethyl acetate/hexane; [1]H NMR (300 MHz, Acetone-D_6); 8.80 Hz, (s, 1H), 8.02 Hz, (dd, 1H), 7.95 Hz, (dd, 1H), 7.68 Hz, (dd, 1H), 7.58 Hz, (m, 2H), 7.46 Hz, (d, 2H), 7.21 Hz, (d, 1H), 6.87 Hz, (dd, 1H), 4.31 Hz (q, 2H), 1.31 Hz (t, 3H).

The following compounds were prepared according to the method of Example **211**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
212		28		0.41 (Hexane/ ethyl acetate 4:1)	

Example 213

Ethyl 3-bromo-6-hydroxy-1-(4-methoxybenzyl)indole-2-carboxylate

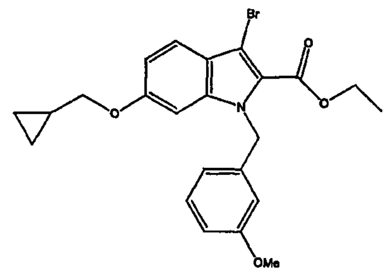


A 0.5 mL ethanol/ 0.5 mL HF solution of 44 mg ethyl 6-(benzoyloxy)-1-(4-methoxybenzyl)indole-2-carboxylate (Example **20**, 0.1 mmol) was cooled to 0°C in a 10 mL round-bottom flask and stir bar. To this stirring solution was added 0.3 mL of NaOEt 1.0 M in ethanol dropwise. The contents were then brought to reflux and maintained for 2 hours. The content were then cooled to room temperature and quenched with water then acidified with 1 N HCl. The reaction contents were then extracted with 3x5 mL of ethyl acetate, dried with Na_2SO_4 to yield 0.42 mg (95% yield) of an off white solid. The product

had a Rf of 0.17 20% ethyl acetate/hexane; ^{1}H NMR (300 MHz, Acetone-D_6); 8.68 Hz (s, 1H), 7.47 Hz (d, 1H), 7.19 Hz (t, 1H), 6.87 Hz (m, 2H), 6.79 Hz (dd, 1H), 6.67 Hz (s, 1H), 6.62 Hz (dt, 1H), 5.76 Hz (s, 2H), 4.35 Hz (q, 2H), 3.40 Hz (s, 3H), 1.37 Hz (t, 3H).

Example 214

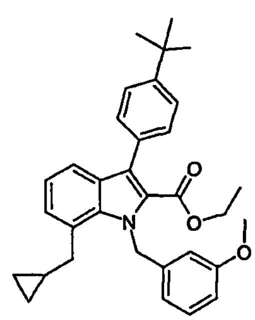
Ethyl 3-bromo-6-(cyclopropylmethoxy)-1-(3-methoxybenzyl)indole-2-carboxylate



To a dry 5 mL round-bottom flask and stir bar was charged with 3.0 mg of NaH (0.12 mmol) followed by addition of 0.2 mL of DMF and cooled to 0 C. To the heterogeneous solution was added a 0.3 ml 42 mg DMF solution of ethyl 3-bromo-6-hydroxy-1-(4-methoxybenzyl)indole-2-carboxylate (Example **213**, 0.1 mmol). The solution was maintained at 0°C for 20 minutes after which bromomethyl cyclopropane was added via syringe and the reaction contents were warmed to rt. and stirred overnight. The reaction was quenched with water then acidified followed by extraction with ethyl acetate and concentration *in vacuo* to yield 30.0 mg (61.05 yield) of an off white solid. The product had a Rf of 0.58 20% ethyl acetate/hexane ; mass spectroscopy gave M^+ of 459.6 (calc'd exact mass for $C_{23}H_{24}BrNO_4$ = 458.34)

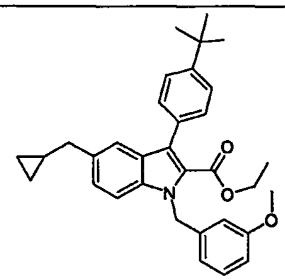
Example 215

Ethyl-3-(4-t-butylphenyl)-7-cyclopropylmethyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



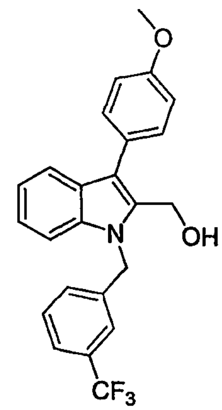
Aluminum chloride (0.24 g, 2 eq.) was suspended in dichloromethane (20 mL) and cooled to 0 °C. Borane-t-butylamine complex (0.14 g, 1.8 eq.) was added slowly, and the mixture was stirred for 30 minutes. A solution of ethyl-3-(4-t-butylphenyl)-7-(cyclopropyl)carbonyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **201**, 0.405 g, 0.9 mmol.) in dichloromethane (5 mL) was added, and the reaction was stirred for two hours. The mixture was quenched with water and diluted with dichloromethane. The organic layer was washed with 1N HCl and saturated sodium bicarbonate, dried over sodium sulfate, then purified by flash chromatography over silica to give 0.26 g (62%.) The desired product had: ^{1}H NMR (300 MHz, $CDCl_3$) 7.21-7.4 (m, 5 H), 7.11 (d, 1 H), 7.02 (t, 1 H), 6.95 (t, 1 H), 6.59 (d, 1H), 6.35 (m, 2 H), 5.9 (s, 2 H), 3.9 (q, 2 H), 3.58 (s, 3 H), 2.75 (d, 2 H), 1.26 (s, 9 H), 0.85 (t, 3 H), 0.4 (m, 2 H), 0.02 (m, 2H).

The following compounds were prepared according to the method of Example **215**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
216		crude			

Example 217

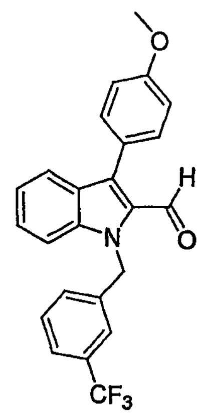
(3-(4-Methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indol-2-yl)methan-1-ol



To a stirred solution of ethyl 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]-methyl}indole-2-carboxylate, prepared by the method described in WO94/14434 (1.20 g, 2.65 mmol), in tetrahydrofuran was added a 2.0 M solution of LiBH4 in tetrahydrofuran (2.65 mL, 5.29 mmol). The resulting mixture was heated to reflux for 18 h. The reaction was cooled to RT and then to 0°C. A 1.0 M solution of LiAlH4 in tetrahydrofuran (4 mL, 4 mmol) was added and the reaction stirred another 2 h. The reaction was quenched by the addition of water then 1.0 M HCl in water. The resulting mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to a residue. Flash chromatography of the residue on silica in a 2:1 to 1:2 hexane:ethyl acetate gradient yielded 650 mg (60%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65-7.46 (m, 6H), 7.39-7.34 (m, 1H), 7.32-7.25 (m, 1H), 7.17-7.02 (m, 4H), 5.68 (s, 2H), 5.40 (s, 2H), 4.59 (s, 2H), 3.81 (s, 3H) ppm; R_f = 0.41 (2:1 hexane:ethyl acetate (v/v)).

Example 218

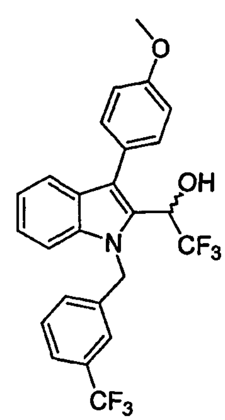
3-(4-Methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indole-2-carbaldehyde



To a solution of (3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indol-2-yl)methan-1-ol (Example **217**, 600 mg, 1.45 mmol) in dichloromethane (20 mL) was added Dess-Martin Periodinane (1.2 g, 2.9 mmol) and the resulting yellow solution was stirred for 30 min at RT. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (10 mL) and saturated aqueous sodium thiosulfate (10 mL). The resulting mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated to an orange solid. The solid was washed with Et2O and collected by filtration to yield 257 mg (45%) of a pale yellow solid. R_f = 0.66 (4:1 hexane:ethyl acetate (v/v)).

Example 219

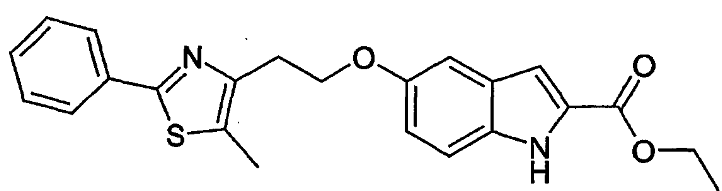
2,2,2-Trifluoro-1-(3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indol-2-yl)ethan-1-ol



To a solution of 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indole-2-carbaldehyde (Example **218**, 200 mg, 0.49 mmol) in tetrahydrofuran (5 mL) was added a 0.5 M solution of TMSCF3 in tetrahydrofuran (4.9 mL, 2.4 mmol). The resulting solution was cooled to 0°C and a 1.0 M solution of TBAF in tetrahydrofuran (0.10 mL, 0.10 mmol) was added. The mixture was stirred for 10 min at 0°C and then let warm to RT and quenched by the addition of water. The resulting mixture was extracted with tetrahydrofuran, adsorbed onto silica, and purified by flash chromatography on silica in 4:1 hexane:ethyl acetate (v/v) to yield 49 mg (21%) of an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60-7.26 (m, 6H), 7.22-7.01 (m, 6H), 5.81 (s, 2H), 3.83 (s, 3H); mass spectroscopy gave MH$^+$ = 480.2 (calc'd exact mass for C25H19F3NO2 = 479.13).

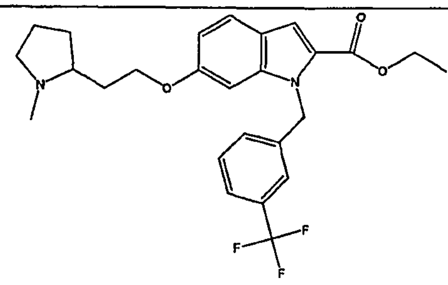
Example 220

Ethyl 5-[2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)ethoxy]-1*H*-indole-2-carboxylate



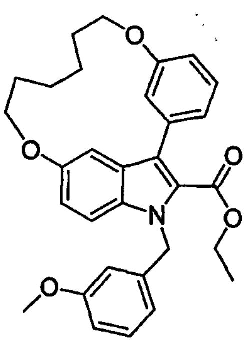
A solution of ethyl 5(hydroxy)-1*H*-indole-2-carboxylate (991 mg, 4.83 mmol) and 2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)ethanol (1.06 g, 4.83 mmol) in tetrahydrofuran (30 + 5 mL rinse) was added to a stirred mixture of triphenylphosphine (1.3 g, 4.9 mmol) and 1,1'-(azodicarbonyl)dipiperidine (1.2 g, 4.9 mmol) in tetrahydrofuran (10 mL). The reaction was stirred for 48 h and then diluted with ethyl acetate (200 mL). This solution was washed successively with water, 10% hydrochloric acid, and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 25% ethyl acetate/hexane gave 1.04 g (53%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D$_6$) □ 10.40-10.55 (br s, 1 H), 7.89-7.95 (m, 2 H), 7.38-7.49 (m, 4 H), 7.19 (d, 1 H), 7.06-7.09 (m, 1 H), 6.95 (dd, 1 H), 4.30-4.40 (m, 4 H), 3.20 (t, 2 H), 2.51 (s, 3 H), 1.35 (t, 3 H); mass spectrometry gave MH$^+$ = 407.1 (calc'd exact mass for $C_{23}H_{22}N_2O_3S$ = 406.14).

The following compounds were prepared according to the method of Example **220**:

Ex. No.	Structure	Yield [%]	MS [M+ H+]	Rf	mp [°C]
221		36	475.3	0.1 (Hexane/ ethyl acetate 7:3)	

Example 222

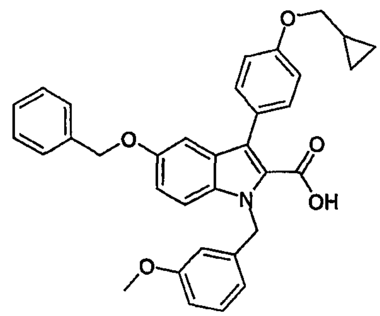
Ethyl 19-aza-19-[(3-methoxyphenyl)methyl]-7,14-dioxatetracyclo-[13.5.2.1<2,6>.0<18,21>]tricosa-1(20),2,4,6(23),15(22),16,18(21)-heptaene-20-carboxylate



To a solution of ethyl 5-hydroxy-3-(3-hydroxyphenyl)-1-[(3-methoxyphenyl)-methyl]indole-2-carboxylate (Example **118**, 237 mg, 0.57 mmol) in acetone (20 mL) was added potassium carbonate (200 mg, 1.45 mmol) and 1,6-dibromohexane (0.079 mL, 0.52 mmol). The resulting mixture was heated to reflux for 48 h, cooled to RT, concentrated and partitioned between ethyl acetate and water. The organic layer was collected and the aqueous layer was extracted with ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate and concentrated to 25 mg (9%) of an oil. Mass spectroscopy gave $MH^+ = 500.2$ (calc'd exact mass for $C_{31}H_{33}NO_5 = 499.24$); TLF $R_f = 0.22$ (hexane/ethyl acetate 2:1).

Example 229

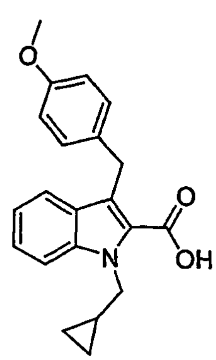
5-(Benzyloxy)-3-[4-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylic acid



1 M Aqueous sodium hydroxide (1 mL) was added to a stirred solution of ethyl 5-(benzyloxy)-3-[4-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **61**, 100 mg, 0.178 mmol) in methanol (1 mL). The reaction was warmed (50 °C) and stirring was continued for 18 h. After cooling the reaction was diluted with water (20 mL) and then the solution was adjusted to pH = 2 using 1 M hydrochloric acid. The product was extracted with ethyl acetate (3x20 mL) and then the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 50% ethyl acetate/hexane gave 38.4 mg (40%) of the desired product as a pure white solid (mp = 185-187 °C). The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.48 (m, 8 H), 6.89-7.17 (m, 3 H), 6.65-6.78 (m, 2 H), 5.83 (s, 2 H), 5.05 (s, 2 H), 3.84 (d, 2 H), 3.68 (s, 3 H), 1.25-1.35 (m, 1 H), 0.57-0.67 (m, 2 H), 0.31-0.41 (m, 2 H); mass spectroscopy gave MH^+ = 534.1 (calcd exact mass for $C_{34}H_{31}NO_5$ = 533.22).

Example 230

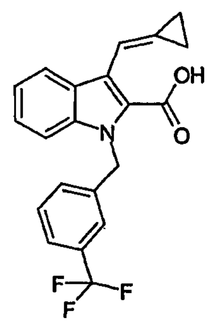
1-(Cyclopropylmethyl)-3-[(4-methoxyphenyl)methyl]indole-2-carboxylic acid



1.0 M Aqueous sodium hydroxide (4 mL), methanol (2 mL), and potassium hydroxide (5 pellets) were added to a stirred solution of Example **42** (181 mg, 0.499 mmol) in tetrahydrofuran (4 mL). The resulting mixture was heated to reflux for 18 h, cooled to RT, and acidified with 1.0 M hydrochloric aced. The resulting mixture was extracted with ethyl acetate and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give 122 mg (72%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65-7.53 (m, 2H), 7.30-7.23 (m, 1H), 7.16-7.11 (m, 2H), 7.07-7.00 (m, 1H), 6.79-6.74 (m, 2H), 4.44 (d, J = 7.0 Hz, 2H), 4.35 (s, 2H), 3.66 (s, 3H), 1.25-1.15 (m, 1H), 0.40-0.30 (m, 4H); mass spectroscopy gave MH$^+$ = 336.0 (calcd exact mass for $C_{21}H_{21}NO_3$ = 335.15), mp = 162-163°C.

Example 231

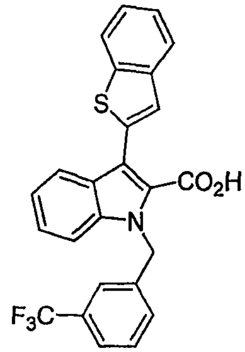
3-(Cyclopropylidenemethyl)-1-[3-(trifluoromethyl)benzyl] -1H-indole-2-carboxylic acid



The compound was prepared from ethyl 3-(cyclopropylidenemethyl)-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate (Example **182**) using the method described in Example **229**, except 6N aqueous sodium hydroxide solution was used with tetrahydrofuran as a co-solvent. Flash chromatography of the residue over silica gel using 50% ethyl acetate/hexane gave the title compound (57%) as a pale yellow solid (mp = 148-150 °C). The product had: ^{1}H NMR (300 MHz, acetone-d_6) δ 11.70 (s, 1 H), 8.16 (d, 1 H), 7.70 (s, 1 H), 7.56-7.46 (m, 4 H), 7.35-7.27 (m, 2 H), 7.19-7.15 (m, 1 H), 5.98 (s, 2 H), 1.58-1.53 (m, 2 H), 1.33-1.28 (m, 2 H); mass spectroscopy gave MH$^+$ = 372.1 (calcd exact mass for $C_{21}H_{16}F_3NO_2$ = 371.11).

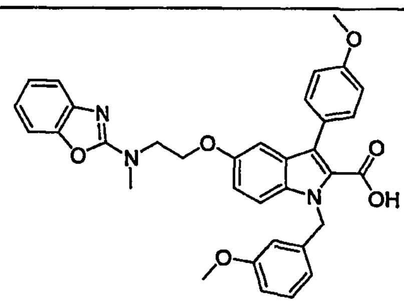
Example 232

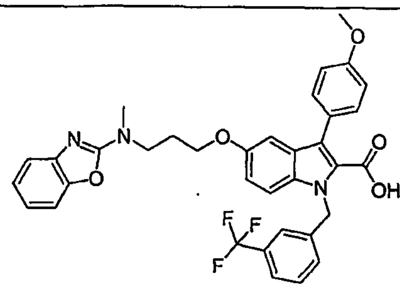
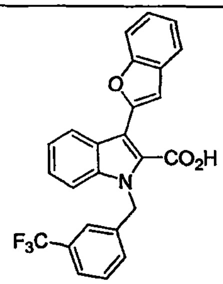
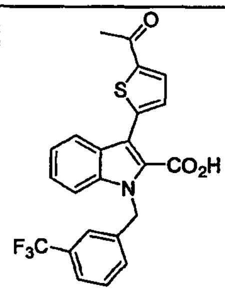
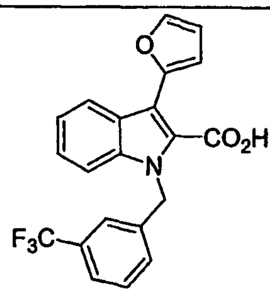
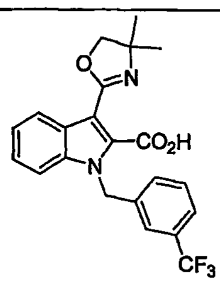
3-(Benzothien-2-yl)-1-[3-(trifluoromethyl)benzyl)-indole-2-carboxylic acid

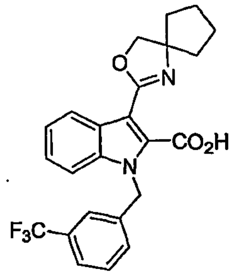
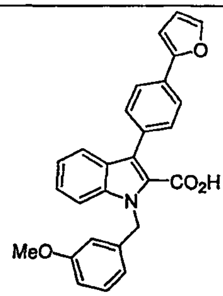
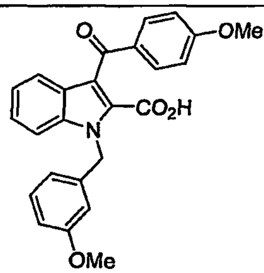
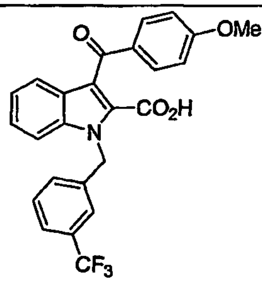
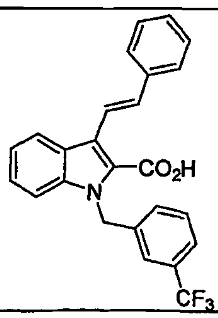


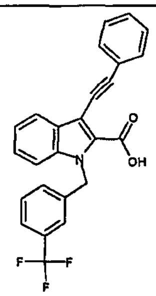
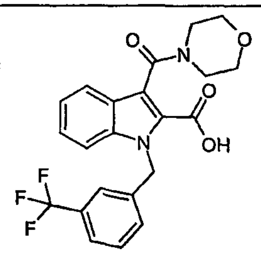
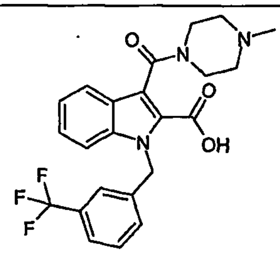
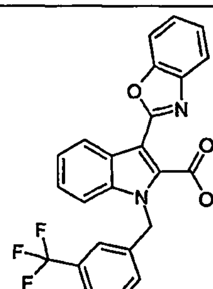
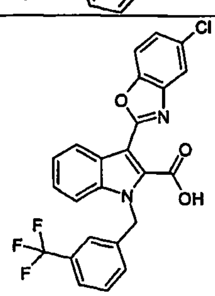
A mixture of 3 N aq. potassium hydroxide (0.85 mL), Example **62** (100 mg, 0.210 mmol), tetrahydrofuran (0.75 mL) and ethanol (0.75 mL) was refluxed for 2 h. The resulting mixture was diluted with ethyl acetate and acidified with 2 N hydrochloric acid. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated to afford 67 mg (71%) of product as a white solid. Rf = 0.40 (9/1 dichloromethane/methanol); LRMS (+esi) obs'd: 452.0; calcd 451.1, m.p. 243-246°C.

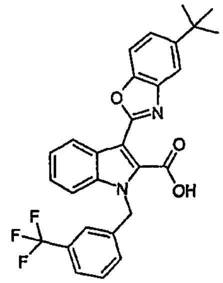
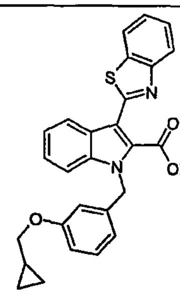
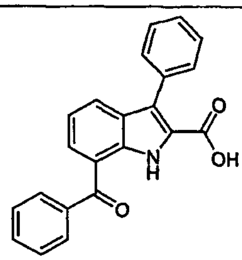
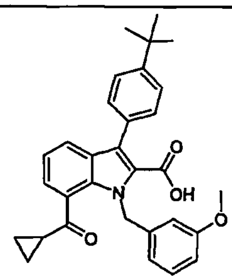
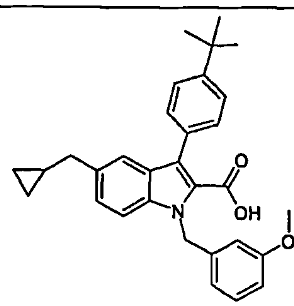
The following compounds were prepared according to the methods of Examples **229, 230, 232** or **232**:

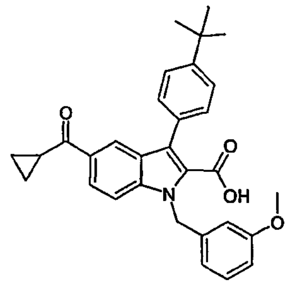
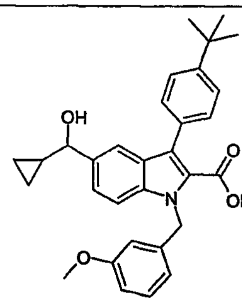
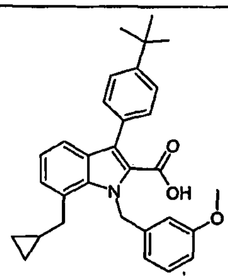
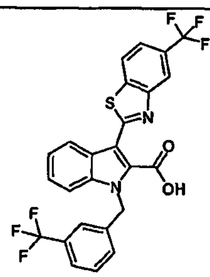
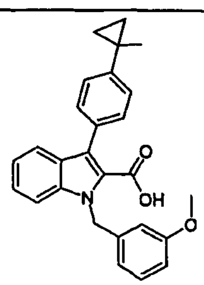
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
233		95	578.2	0.26 (CH_2Cl_2 / methanol 95:5)	

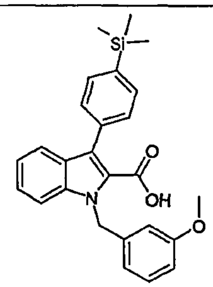
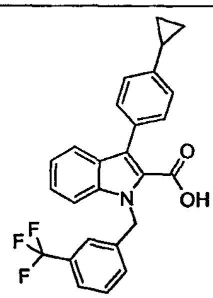
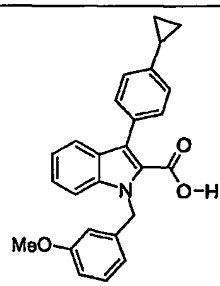
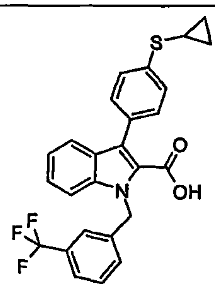
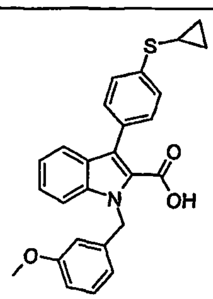
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
234		55	630.3	0.71 (ethyl acetate)	
235		33	436.0	0.39 (CH_2Cl_2/ methanol 9:1)	211 – 214
236		76	444.1	0.22 (CH_2Cl_2/ methanol 9:1)	212 – 214
237		81	386.1	0.34 (CH_2Cl_2/ methanol 9:1)	172 – 173
238		20 (2 steps)	417.2	0.32 (CH_2Cl_2/ methanol 9:1)	

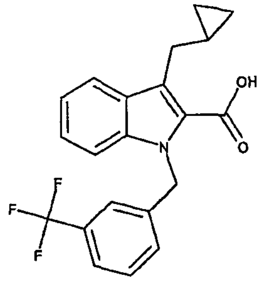
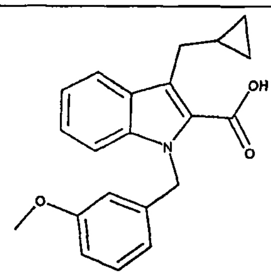
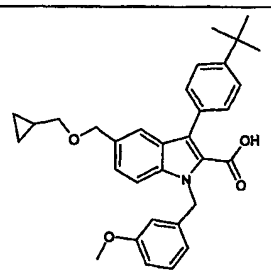
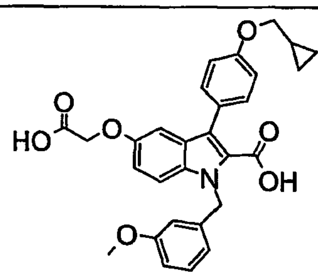
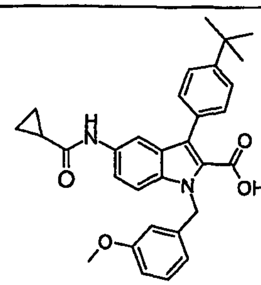
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
239		7 (3 steps)	443.2	0.38 (CH_2Cl_2/ methanol 9:1)	
240		57	424.1	0.20 CH_2Cl_2 / methanol 95:5)	190 – 192
241		65	416.1	0.24 (CH_2Cl_2/ methanol 9:1)	68 - 69
242		77	454.0	0.29 (CH_2Cl_2/ methanol 9:1)	215 - 216
243		2	420.4 (-FIMS)	0.42 (CH_2Cl_2/ methanol 9:1)	183 - 185

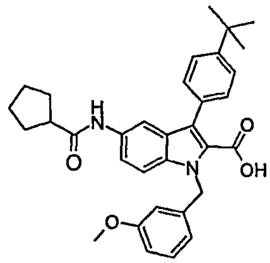
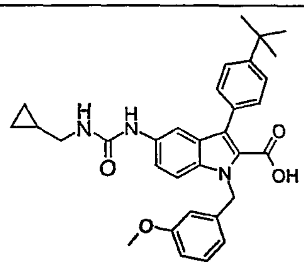
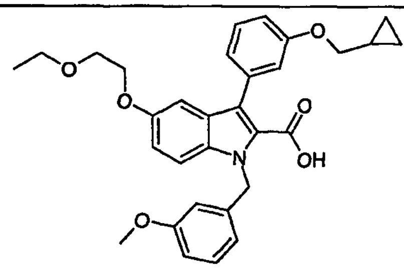
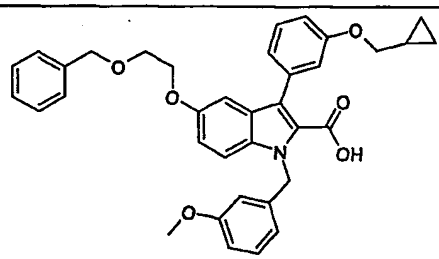
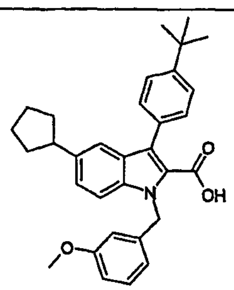
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
244		47	419 (M+)	0.39 (CH_2Cl_2/ methanol 9:1)	165 - 167
245		28			
246		11	446		
247		54	437		
248		32	471		

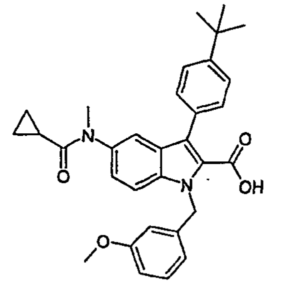
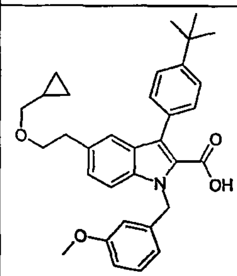
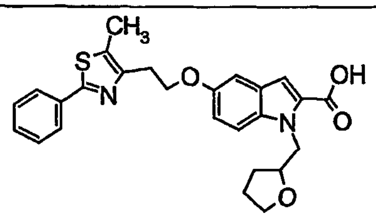
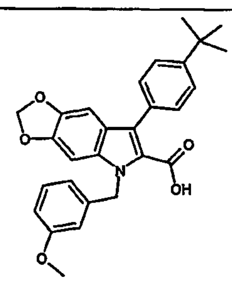
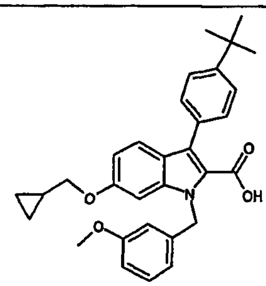
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf (TLC)	mp [°C]
249		48	493		
250		34	n.d.		
251		72	342		
252		79			
253		93			

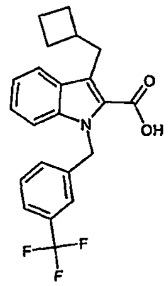
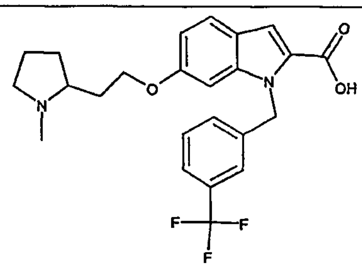
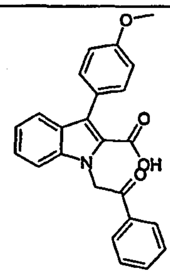
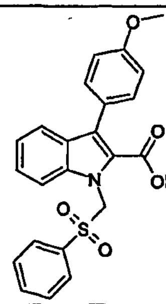
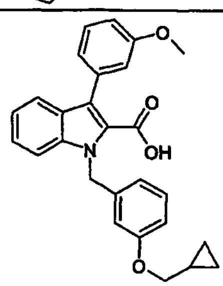
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf (TLC)	mp [°C]
254		88			
255		19			
256		51			
257		23	521		
258		25	412		

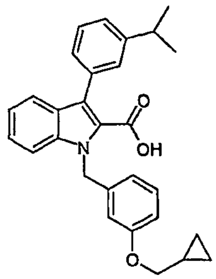
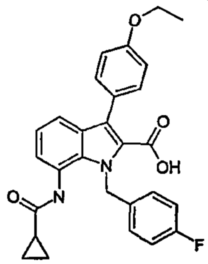
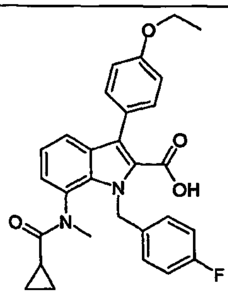
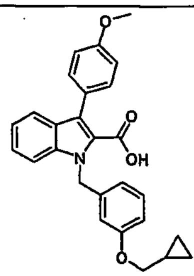
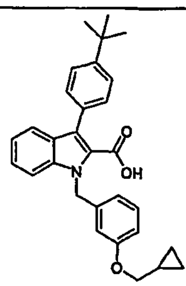
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf (TLC)	mp [°C]
259		35	402		
260		90	436		
261		92	398		
262		96	468		
263		93	430		

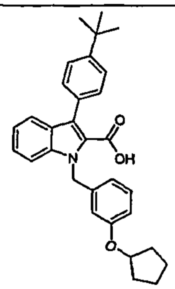
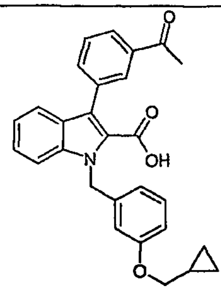
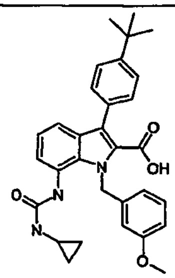
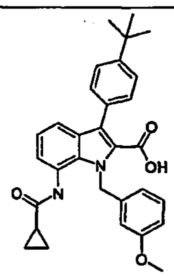
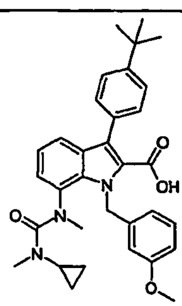
Ex. No.	Structure	Yield [%]	MS $[M+H^+]$	Rf (TLC)	mp [°C]
264		65	374.4	0.25 (Hexane / Et_2O 80:20)	174-175
265		70	336.2	0.10 (Hexane / ethyl acetate 90:10)	165-167
266		69	498.6	0.10 (45:45:10 hexane / ethyl acetate/ methanol)	79 - 80
267		9	502		
268		38	497.3		194-196

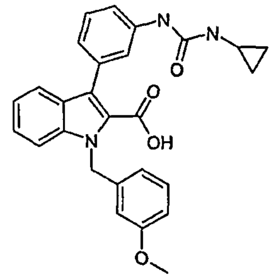
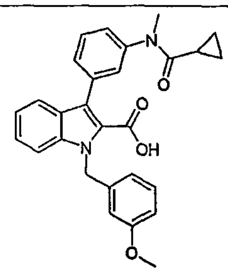
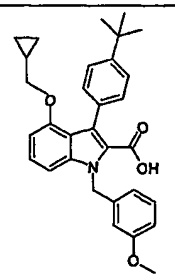
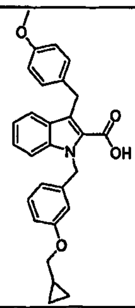
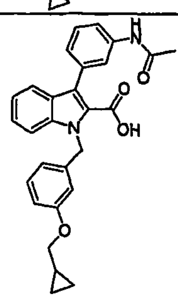
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
269		64	525.3		154-156
270		46	526.3		141-142
271		91	516.2	0.15 (2:1 hexane-ethyl acetate)	
272		65	578.2	0.15 (2:1 hexane-ethyl acetate)	
273		56	482.2		192-193

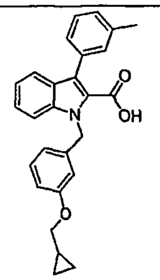
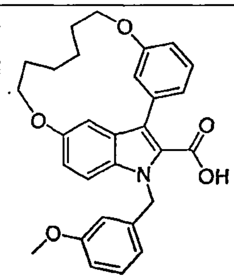
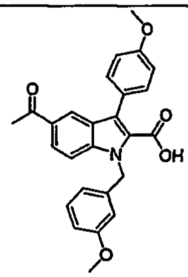
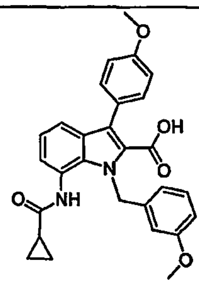
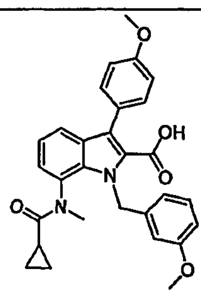
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf (TLC)	mp [°C]
274		90	511.3		219-222
275		75	512.2		
276		66	463.2		
277		42	458.1	0.5 (2.5% methanol /CH2Cl2	179.1 - 179.7
278		99	386.5 [M-H+]		

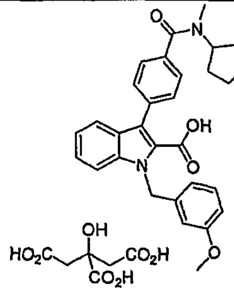
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf (TLC)	mp [°C]
279		45	484.2	0.13 (20% ethyl acetate / hexane)	
280		44	447.3	0.29 (5% methanol / CH_2Cl_2)	
281		85	386		
282		100			166 - 168
283		59	428		

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
284		78	440		204
285		88	473		250
286		77	487		128
287		76	428		168
288		82	454		120

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
289		70	468		159
290		74	440		103
291		50	512		168 (dec.)
292		95	497		151
293		66	540		112-115 (dec.)

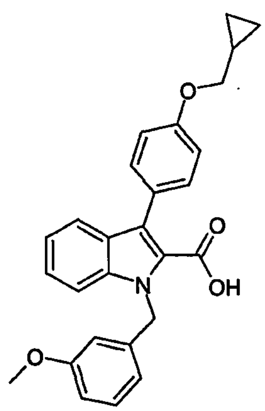
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
294		45	456		110 (dec.)
295		71	455		200
296		75	484		162
297		86	442		168-170
298		20	455.0		122-123

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf (TLC)	mp [°C]
299		79	412.1		58-60
300		50	472.2		79-80
301		87	430.2	0.29 (ethyl acetate)	190d
302		76	471.0		210d
303		63	485.1		98d

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
304		89	483.3		169d

Example 305

3-[4-(Cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylic acid

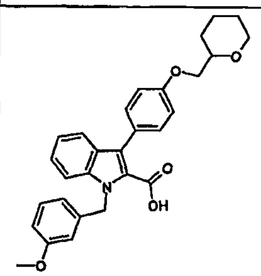
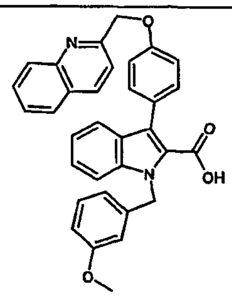
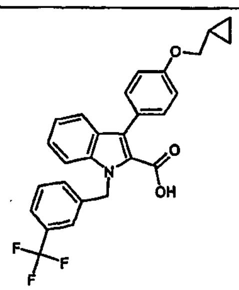


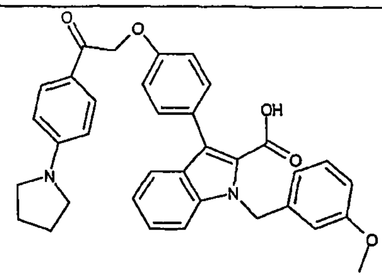
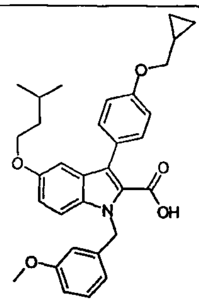
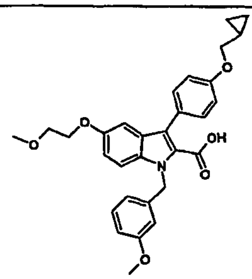
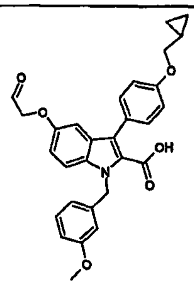
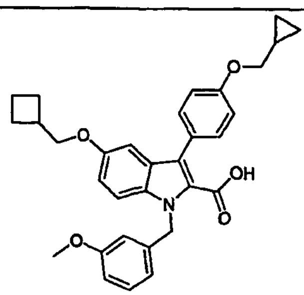
Ethyl 3-[4-hydroxyphenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **121**, 21 mg, 0.05 mmol), bromomethylcyclopropane (14 mg, 0.10 mmol), potassium carbonate (21 mg, 0.15 mmol), and potassium iodide (catalytic amount) were heated (90 °C) in DMF (0.8 mL) for 15 hrs. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane (2 mL). The mixture was filtered and then preparative thin layer chromatography of the filtrate (ethyl acetate:hexane = 1:3) afforded the desired intermediate (31%).

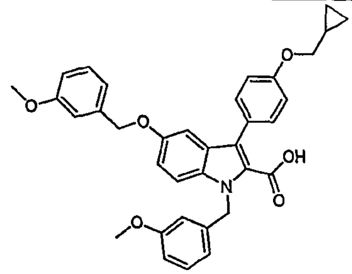
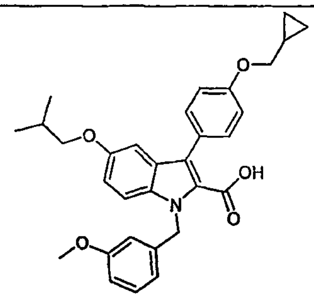
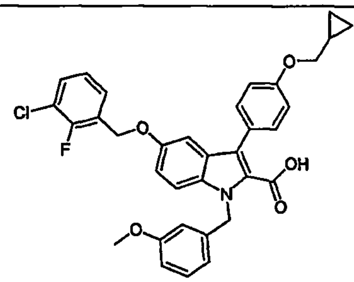
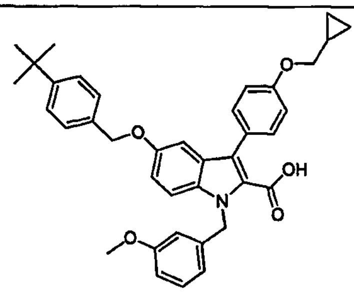
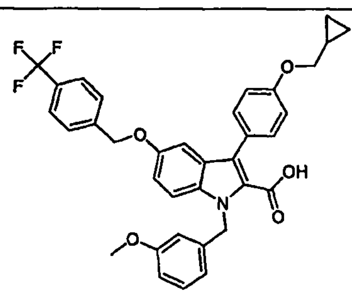
Ethanol (300 µL) was added to the intermediate (7 mg). A 2 N solution of potassium hydroxide in ethanol/water (1:1, 200 µL) was added and the mixture was heated (60 °C) for 2 hrs. The mixture was cooled to rt and put into an ice bath. 2 N

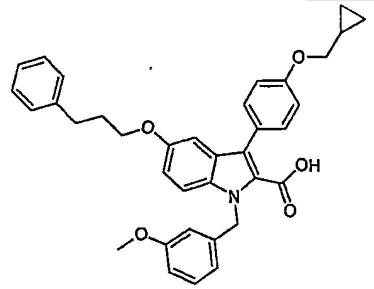
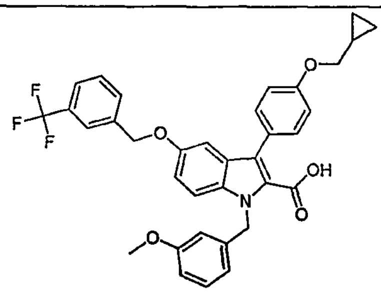
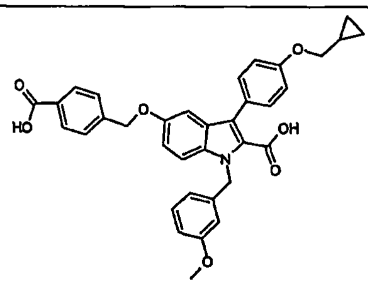
hydrochloric acid (210 μL) was added and a white precipitate formed. The solvent was removed under reduced pressure and the residue was dissolved in 2 mL of dichloromethane. The mixture was filtered and then preparative thin layer chromatography of the filtrate (ethyl acetate:methanol = 95:5) gave 4 mg (61%) of desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65-7.60 (m, 12 H), 5.75 (s, 2 H), 3.84 (d, 2 H), 3.68 (s, 3 H), 1.25 (m, 1 H), 0.65 (m, 2 H), 0.40 (m, 2 H); mass spectroscopy (negative ion mode) gave $[M-H]^-$ = 426.2 (RT = 4.73, calcd exact mass for $C_{27}H_{25}NO_4$ = 427.18).

The following compounds were prepared according to the method of Example 305:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	RT (TLC)	mp [°C]
306		31	472.2	4.49	
307		24	515.2	4.14	
308		35	466.0	5.01	

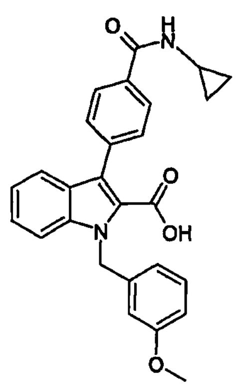
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	RT (TLC)	mp [°C]
310		19	561.2	4.06	
311		35	542.2	4.97	
312		32	500.2	3.40	
313		15	484.2	3.41	
314		41	510.2	3.88	

Ex. No.	Structure	Yield [%]	MS [M+H+]	RT (TLC)	mp [°C]
315		38	562.2	3.76	
316		32	498.2	3.85	
317		40	584.2	3.90	
318		42	588.3	4.14	
319		37	600.3	3.94	

Ex. No.	Structure	Yield [%]	MS [M+H+]	RT (TLC)	mp [°C]
320		33	560.2	3.97	
321		34	600.2	3.93	
322		19	576.2	3.29	

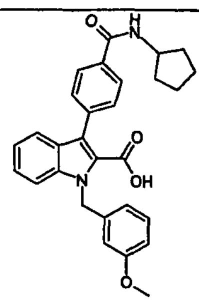
Example 323

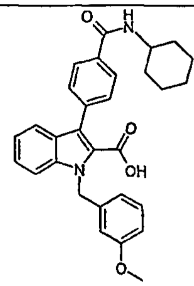
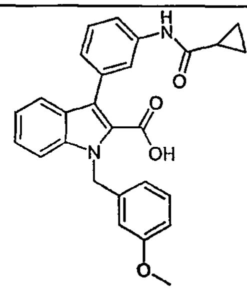
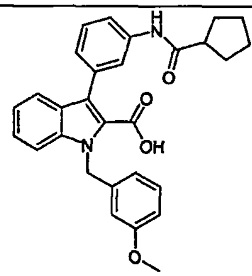
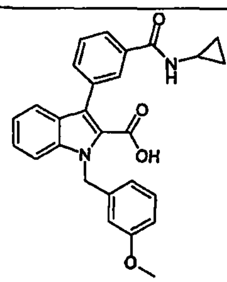
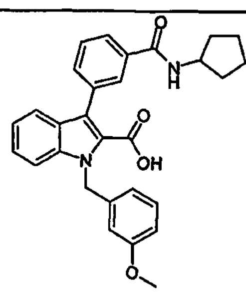
3-[4-(N-cyclopropylcarbamoyl)phenyl]-1-[(3-methoxyphenyl)methyl]indole-2-carboxylic acid



To a 25 mL round-bottomed flask at rt was charged with 4-{2-(ethoxycarbonyl)-1-[(3-methoxyphenyl)methyl]indol-3-yl}benzoic acid (Example 98, 270 mg, 0.63 mmol), tetrahydrofuran (2 mL) and one drop of *N,N*-dimethylformamide. Oxalyl chloride (240 mg, 0.16 mL, 1.89 mmol) was added to the above mixture dropwise. After 1 hour, the reaction mixture was concentrated and re-dissolved in tetrahydrofuran (2 mL) and cyclopropylamine (359 mg, 6.3 mmol) was added. After 10 minutes at rt, aqueous sodium hydroxide (3 N) was added to the reaction mixture and enough methanol was added to make the mixture one phase. The resulting solution was refluxed for 1 hour before it was cooled to rt and acidified with hydrochloric acid (1N) and extracted with ethyl acetate (25 mL). The organic layer was washed with water, brine and dried over anydrous sodium sulfate. The solution was concentrated *in vacuo* to give a white solid which was triturated with diethyl ether to provide 3-[4-(N-cyclopropylcarbamoyl)phenyl]-1-[(3-methoxyphenyl)methyl]indole-2-carboxylic acid as a white solid (142 mg, 51%): mp 237 °C; MS (electrospray, MH^+) calcd for $C_{27}H_{25}N_2O_4$ 441, found 441; ^1H NMR (DMSO-d^6) δ 13.1 (br s, 1H), 8.48 (d, J = 4.0 Hz, 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H), 7.30-7.37 (m, 1H), 7.12-7.22 (m, 2H), 6.79 (dd, J = 8.2, 2.5 Hz, 1H), 6.69 (dd, 1H), 6.62 (d, J = 7.6 Hz, 1H), 5.83 (s, 2H), 3.68 (s, 3H), 2.85-2.89 (m, 1H), 0.56 – 0.64 (m, 2H), 0.65-0.75 (m, 2H).

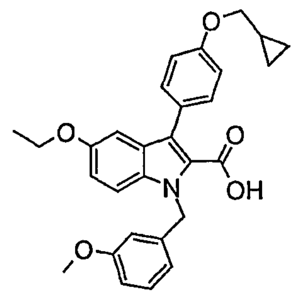
The following compounds were prepared according to the method of Example 323.

Ex. No.	**Structure**	**Yield [%]**	**MS [M+H$^+$]**	**Rf (TLC)**	**mp [°C]**
324		82	469		230

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf (TLC)	mp [°C]
325		30	483		245
326		41	441		
327		97	469		133 (dec.)
328		86	441		204
329		82	469		108

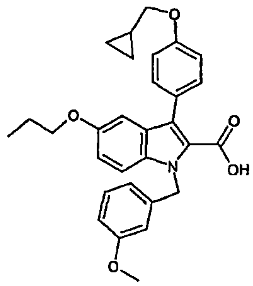
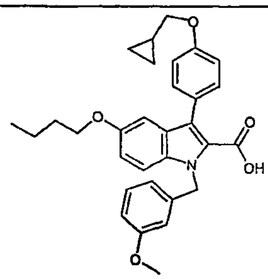
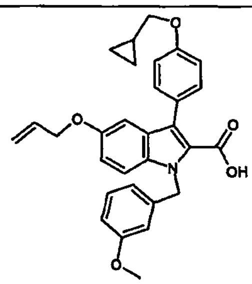
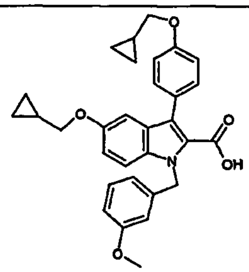
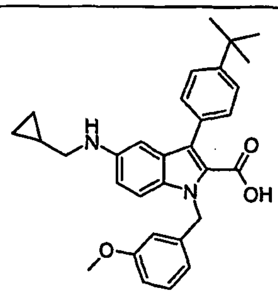
Example 330

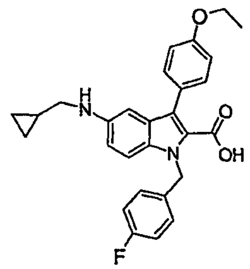
3-[4-(Cyclopropylmethoxy)phenyl]-5-ethoxy-1-(3-methoxybenzyl)-1H-indole-2-carboxylic acid



Water (5 *u*L) was added to a cooled (0 °C) and stirred suspension of potassium *t*-butoxide (90 mg, 0.80 mmol) in ethyl ether (5 mL). The slurry was stirred for 5 min and then a solution of ethyl 3-[4-(cyclopropylmethoxy)phenyl]-5-ethoxy-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **144**, 52 mg, 0.10 mmoL) in ethyl ether (2 + 1 mL rinse) was added. The mixture was warmed to rt and stirred for 16 h. The solution was adjusted to pH = 7 with 1 M hydrochloric acid and diluted with ethyl acetate (50 mL). This mixture was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by preparative TLC, using 1:1 ethyl acetate/hexane as the eluent, to afford 7.0 mg (14%) of desired product. The product had: ^{1}H NMR (300 MHz, acetone-D$_6$) δ 7.45-7.37 (m, 3 H), 7.18 (t, 1 H), 6.99-6.91 (m, 4 H), 6.77 (dd, 1 H), 6.70 (m, 2 H), 5.85 (d, 2 H), 3.99-3.86 (m, 4 H), 3.69 (s, 3 H), 1.36-1.28 (m, 4 H), 0.63-0.59 (m, 2 H), 0.39-0.37 (m, 2 H); mass spectroscopy gave MH$^+$ = 472.2 (calcd exact mass for $C_{29}H_{29}NO_5$ = 471.20).

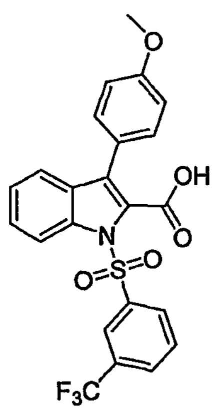
The following compounds were prepared according to the method of Example **330:**

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (tlc)	mp [°C]
331		30	486.2	0.52 (2:1 hexane-ethyl acetate)	
332		39	500.2	0.52 (2:1 hexane-ethyl acetate)	
333		51	484.2	0.52 (2:1 hexane-ethyl acetate)	
334		29	498.2	0.52 (2:1 hexane-ethyl acetate)	
335		55	483.3		180-181

Ex. No.	Structure	Yield [%]	MS [M+H⁺]	Rf (tlc)	mp [°C]
336		48	516.2	0.17 (2:1 hexane-ethyl acetate)	

Example 337

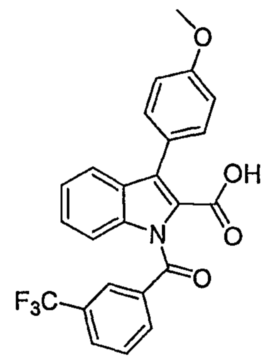
3-(4-Methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]sulfonyl}indole-2-carboxylic acid



tert-Butyl 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]sulfonyl}indole-2-carboxylate (Example 27, 45 mg, 0.085 mmol) was dissolved in trifluoroacetic acid (0.4 mL). The resulting mixture was allowed to stir for 5 minutes. The reaction mixture was treated with a saturated aqueous sodium bicarbonate solution and then extracted with ethyl acetate (3x4 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]sulfonyl}indole-2-carboxylic acid as an oil (17 mg, 42%): ^{1}H (acetone-d_6) δ 3.70 (s, 3 H), 6.85-6.89 (m, 2 H), 7.20-7.34 (m, 2 H), 7.47 (dd, *J*=0.6, 8.1 Hz, 1 H), 7.60-7.68 (m, 3 H), 7.83 (br d, 1 H), 8.06 (d, *J*=8.2 Hz, 1 H), 8.63 (m, 2 H); mass spectroscopy HPLC ES MS *m/z* (rel abundance) 476 ($(M+H)^+$, 48%).

Example 338

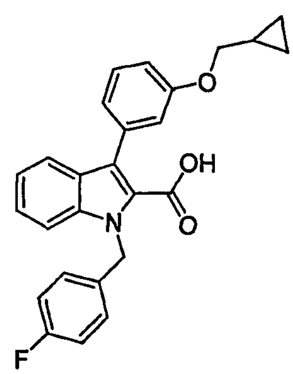
3-(4-Methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]carbonyl} indole-2-carboxylic Acid



tert-Butyl 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]carbonyl}indole-2-carboxylate (Example **226**, 32 mg, 0.065 mmol) was converted using the method described above for Example **230** afford 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)-phenyl]carbonyl}indole-2-carboxylic acid as an oil (2 mg, 7%): ^{1}H NMR (acetone-d_6) 3.84 (s, 1 H), 7.04-7.05 (m, 2 H), 7.32-7.33 (m, 1 H), 7.50-7.52 (m, 4 H), 7.84-7.87 (m, 1 H), 7.99-8.06 (m, 1 H), 8.14-8.19 (m, 1 H), 8.42-8.47 (m, 2 H).

Example 339

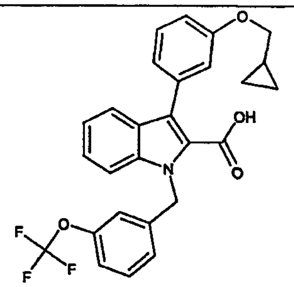
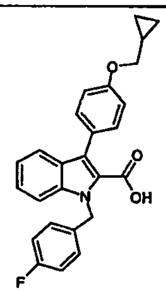
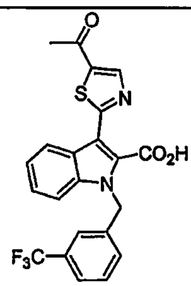
3-[3-(Cyclopropylmethoxy)phenyl]-1-[(4-fluorophenyl) methyl]indole-2-carboxylic Acid

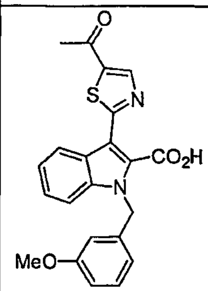
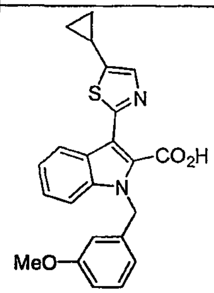
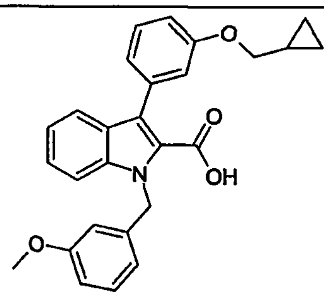
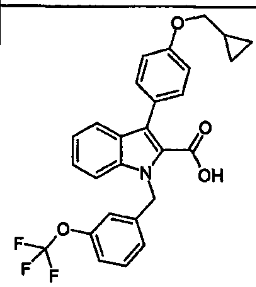


Formic acid (4 mL) was added dropwise to a stirred solution of *tert*-Butyl 3-[3-(cyclopropylmethoxy)phenyl]-1-[(4-fluorophenyl)methyl]indole-2-carboxylate (Example **72**, 431 mg, 0.91 mmol) in dichloromethane (1.0 mL). The reaction was stirred at room temperature for 8 h, then concentrated *in vacuo*. The resulting solids were placed on a pad of silica gel and purified by chromatography (gradient from 30% ethyl acetate/hexane to

100% ethyl acetate) to afford 3-[3-(cyclopropylmethoxy)phenyl]-1-[(4-fluorophenyl)methyl]indole-2-carboxylic acid (324 mg, 85%): mp = 200-202 °C, ^{1}H NMR (acetone-d_6) 0.32-0.37 (m, 2 H), 0.55-0.61 (m, 2 H), 1.21-1.31 (m, 1 H), 3.86 (d, J=7.0 Hz, 2 H), 5.90 (s, 2 H), 6.89-6.93 (m, 1 H), 7.00-7.08 (m, 4 H), 7.11-7.16 (m, 1 H), 7.18-7.24 (m, 2 H), 7.30-7.36 (m, 2 H), 7.52-7.58 (m, 2 H), 11.28 (br s, 1 H); mass spectroscopy gave MH^+ = 416 (60%).

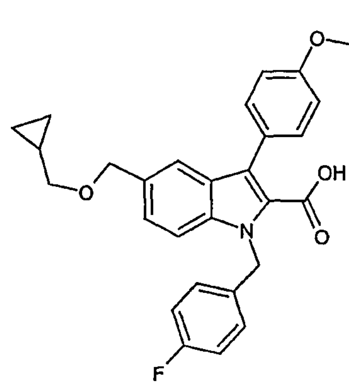
The following compounds were prepared in according to the method of Example 339:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
340		77	482		glass
341		86	416		197-198
342		52 (over 2 steps)	445.2	0.50 (methanol/ CH_2Cl_2 1:9)	

Ex. No.	Structure	Yield [%]	MS $[M+H^+]$	Rf (TLC)	mp [°C]
343		47 (2 steps)	407.2		218 (dec.)
344		5	405.2	0.42 (methanol / CH_2Cl_2 1:9)	
345		76	428.1		147-148
346		82	482.2		204-205

Example 347

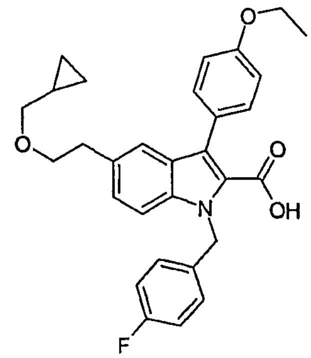
5-[(Cyclopropylmethoxy)methyl]-3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-1H-indole-2-carboxylic acid



Sodium hydride (60% dispersion in mineral oil, 64 mg, 1.60 mmol) was added in portions to a cooled (0 °C) and stirred solution of ethyl 3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-5-(hydroxymethyl)-1H-indole-2-carboxylate (Example **141**, 480 mg, 1.073 mmol) in tetrahydrofuran (10 mL). The mixture was allowed to warm to room temperature over a period of 1 hour. Cyclopropylmethylbromide (216 mg, 1.60 mmol) was added, and the mixture was stirred for 18 hours. The reaction was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2x). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting crude oil was purified by flash chromatography on silica gel eluted on a gradient from 100% hexane to 50% ethyl acetate/hexane. The title compound was obtained as a white solid (50 mg, 10%) with a mp = 171-173 °C. The product had: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.52 (d, 1 H), 7.48-7.47 (m, 1 H), 7.42-7.38 (m, 2 H), 7.34-7.33 (m, 1 H), 7.22-7.18 (m, 2 H), 7.06-6.98 (m, 4 H), 5.89 (s, 2 H), 4.53 (s, 2 H), 4.10 (q, 2 H), 3.27 (d, 2 H), 1.40 (t, 3 H), 1.13-1.01 (m, 1 H), 0.47-0.42 (m, 2 H), 0.25-0.22 (m, 2 H); mass spectroscopy gave MH^+ = 474.2 (calcd exact mass for $C_{29}H_{28}FNO_4$ = 473.20).

Example 348

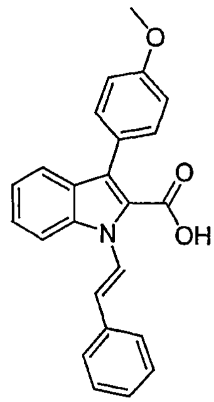
5-[2-(Cyclopropylmethoxy)ethyl]-3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-1*H*-indole-2-carboxylic acid



A solution of ethyl 3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-5-(2-hydroxyethyl)-1*H*-indole-2-carboxylate (Example **133**, 275 mg, 0.596 mmol) in tetrahydrofuran (8 + 2 mL rinse) was added slowly (5 min) to a cooled suspension of sodium hydride (72 mg, 3.0 mmol) in tetrahydrofuran (2 mL). The reaction was stirred for 1 h and then (bromomethyl)cyclopropane (0.29 mmol, 400 mg, 3.0 mmol) was added. The cold bath was removed and the solution was stirred for 18 h. The reaction was quenched by pouring onto ice water (100 mL) and then the solution was adjusted to pH = 7 using 1 M hydrochloric acid. The product was extracted with ethyl acetate (3x70 mL) and then the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. Flash chromatography of the residue over silica gel using 50% ethyl acetate/hexane gave 154 mg (53%) of product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.32-7.50 (m, 4 H), 7.18-7.30 (m, 3 H), 6.97-7.10 (m, 4 H), 5.87 (s, 2 H), 4.09 (q, 2 H), 3.59 (t, 2 H), 3.22 (d, 2 H), 2.88 (t, 2 H), 1.40 (t, 3 H), 0.85-0.10 (m, 1 H), 0.38-0.48 (m, 2 H), 0.13-0.23 (m, 2 H); mass spectroscopy gave MH^+ = 488.0 (exact mass calcd for $C_{30}H_{30}FNO_4$ = 487.22).

Example 349

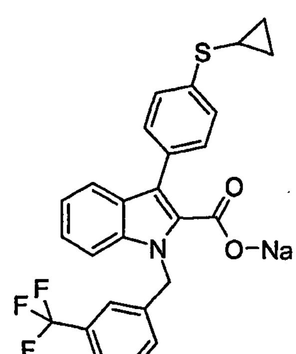
1-((1*E*)-2-Phenylvinyl)-3-(4-methoxyphenyl)indole-2-carboxylate



A 60% suspension of sodium hydride in mineral oil (75 mg, 1.85 mmol) was stirred in DMF (5 mL). To this suspension was added ethyl 3-(4-methoxyphenyl)indole-2-carboxylate (Example **105**, 500 mg, 1.65 mmol). The resulting mixture was stirred for 30 min at RT before (*R*)-styrene oxide was added. The resulting mixture was then heated to 120°C for 18 h. The reaction was cooled to RT, diluted with water, and washed with ethyl acetate. The aqueous layer was collected, acidified with hydrochloric acid, and the resulting suspended solid collected by filtration to yield 311 mg (51%) of a solid. ^1H NMR (300 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.02 (d, J = 14.9 Hz, 1H), 7.87-7.82 (m, 1H), 7.63-7.56 (m, 2H), 7.52-7.36 (m, 6H), 7.36-7.25 (m, 2H), 7.07-7.00 (m, 2H), 6.91 (d, J = 14.9 Hz, 1H), 3.81 (s, 3H).

Example 350

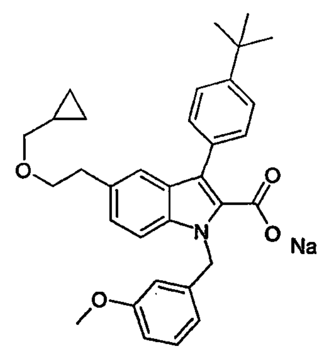
Sodium 3-[4-(cyclopropylsulfanyl)phenyl]-1-[3-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate



To a slurry of sodium hydride (10.8 mg, 0.428 mmol) in 5 ml tetrahydrofuran, was added a solution of 3-(4-Cyclopropylthiophenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indole-2-carb-oxylic acid (Example 77, 100 mg, 0.214 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred at rt for 30 min and filtered to give a 210 mg (100%) of product. ^{1}H NMR (DMSO-D$_6$, δ = 2.48): 7.78 (s, 1H), 7.46 – 7.61 (m, 6 H), 7.29 – 7.35 (m, 3H), 6.95 – 7.05 (m, 2H), 5.71(s, 2H), 2.47 – 2.49 (m, 1H), 1.04 – 1.15 (m, 2H), and 0.58 – 0.63 (m, 2H).

Example 351

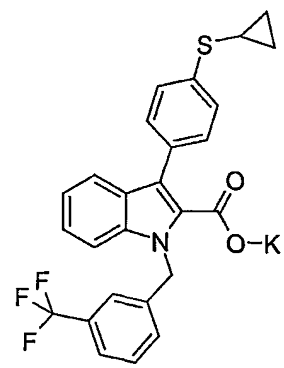
Sodium 3-(4-*tert*-butylphenyl)-5-[2-(cyclopropylmethoxy)ethyl] -1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Sodium hydride (6.8 mg, 0.28 mmol) was added to a cooled (0 °C) and stirred solution of 3-(4-*tert*-butylphenyl)-5-[2-(cyclopropylmethoxy)ethyl]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylic acid (Example **275**, 145 mg, 0.283 mmol) in tetrahydrofuran (10 mL). The cold bath was removed and the mixture was stirred 2 h. Concentration in vacuo left 148 mg (98%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D$_6$) δ 7.63 (d, 2 H), 7.47 (s, 1 H), 7.34 (d, 2 H), 7.18 (d, 1 H), 7.09(dd, 1 H), 6.96 (dd, 1 H), 6.91 (s, 1 H), 6.85 (d, 1 H), 6.69 (dd, 1 H), 5.75 (s, 2 H), 3.66 (s, 3 H), 3.56 (t, 2 H), 3.22 (d, 2 H), 2.84 (t, 2 H), 1.32 (s, 9 H), 0.89-1.05 (m, 1 H), 0.35-0.45 (m, 2 H), 0.07-0.17 (m, 2 H); mass spectroscopy gave M+2H$^+$-Na = 512.2 (calcd exact mass for $C_{33}H_{36}NNaO_4$ = 533.25).

Example 352

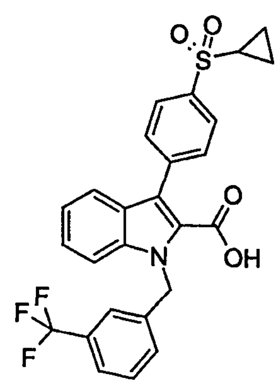
Potassium 3-(4-cyclopropylthiophenyl)-1-{[3-(trifluoromethyl)-phenyl]methyl} indole-2-carboxylate



A solution of 10% potassium hydroxide in methanol:water (1:9, 30 mL) was added to a stirred solution of ethyl 3-(4-cyclopropylthiophenyl)-1-{[3-(trifluoromethyl)-phenyl]methyl}indole-2-carboxylate (Example 262.5 g, 3 mmol) in tetrahydrofuran (3 mL). The reaction was warmed to 50 °C and stirred 18 h. After cooling, the reaction mixture was filtered to leave 50 mg of potassium 3-(4-cyclopropylthiophenyl)-1-{[3-(trifluoromethyl)-phenyl]-methyl}indole-2-carboxylate. ^{1}H NMR (DMSO-D_6) δ 7.80 (s, 1 H), 7.69 – 7.60 (m, 11 H), 5.69 (s, 2 H), 2.27 – 2.31 (m, 1 H), 1.04 – 1.10 (m, 2 H), and 0.58 – 0.63 (m, 2 H).

Example 353

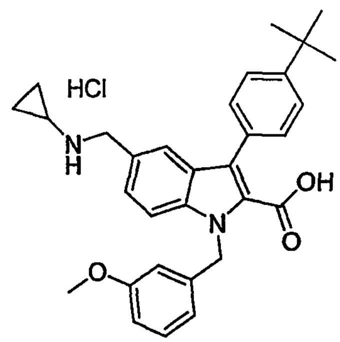
3-[4-(Cyclopropylsulfonyl)phenyl]-1-{[3-(trifluoromethyl)phenyl] methyl}indole-2-carb-oxylic acid



To a solution of 3-(4-Cyclopropylthiophenyl)-1-{[3-(trifluoro-methyl)phenyl]methyl}indole-2-carb-oxylic acid (Example 262) 100 mg, 0.214 mmol) in 10 mL $CHCl_3$, m-CPBA (162 mg, 0.47 mmol) was added at –10 ^{0}C. The reaction was stirred for 2 h and then warmed to rt. The reaction was diluted with dichloromethane and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Flash chromatography of the residue over silica gel using ethyl acetate/hexane gave 70 mg (65%) of product. ^{1}H NMR (DMSO-D_6) δ 13.22 (br s, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.14 –7.12 (m, 10 H), 5.94 (s, 2H), 2.89 – 2.93 (m, 1H), and 1.06 – 1.16 (m, 4H). MS [M-H] = 498 (HPLC/MS).

Example 354

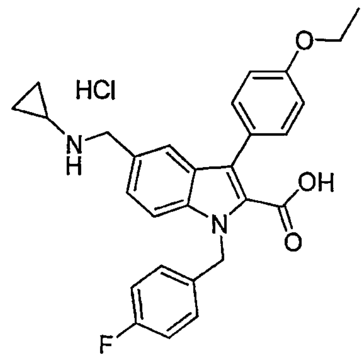
3-(4-*tert*-Butylphenyl)-5-[(cyclopropylmethyl)amino]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylic acid hydrochloride



Ethyl 3-(4-*tert*-butylphenyl)-5-[(cyclopropylmethyl)amino]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **165**, 420 mg, 0.84 mmol) was reacted using the method described for Example **237**. After hydrolysis the solution was adjusted to pH=1 using 1 M hydrochloric acid. The resulting precipitate was collected by filtration, using ethyl ether to wash, to afford 250 mg, (59%) of product. The product had: ^{1}H NMR (300 MHz, CD_3OD) δ 7.71 (d, 1 H), 7.39-7.59 (m, 6 H), 7.16 (dd, 1 H), 6.72-6.80 (m, 1 H), 6.61-6.69 (m, 2 H), 5.84 (s, 2 H), 4.36 (s, 2 H), 3.71 (s, 3 H), 2.68-2.80 (m, 1 H), 1.41 (s, 9 H), 1.15-1.25 (m, 1 H), 0.80-0.96 (m, 4 H); mass spectroscopy gave MH^+-HCl = 483.3 (calcd exact mass for $C_{31}H_{34}N_2O_3$ = 482.26).

Example 355

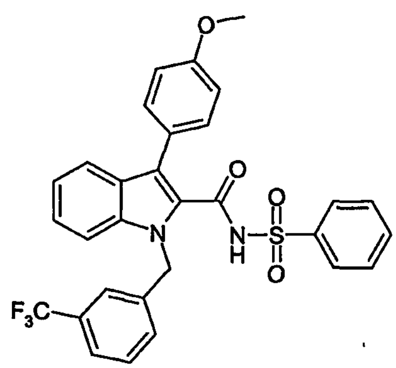
5-[(Cyclopropylmethyl)amino]-3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-1*H*-indole-2-carboxylic acid hydrochloride



Ethyl 5-[(cyclopropylmethyl)amino]-3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-1*H*-indole-2-carboxylate (Example **166**, 470 mg, 0.97 mmol) was converted to 430 mg (90%) of product using the method described for Example **238**. The product had: ^{1}H NMR (300 MHz, CD_3OD) δ 7.70 (d, 1 H), 0.87 (d, 1 H), 7.34-7.44 (m, 3 H), 7.07-7.16 (m, 2 H), 6.92-7.03 (m, 4 H), 5.82 (s, 2 H), 4.35 (s, 2 H), 4.08 (q, 2 H), 2.68-2.77 (m, 1 H), 1.41 (t, 3 H), 1.34-1.43 (m, 1 H), 0.83-0.94 (m, 4 H).

Example 356

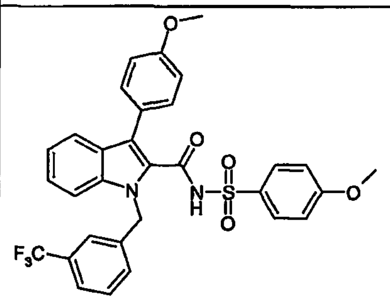
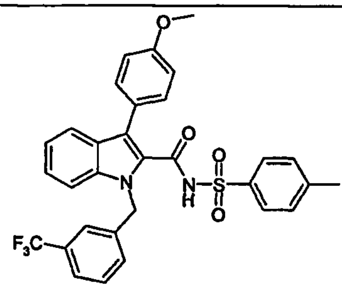
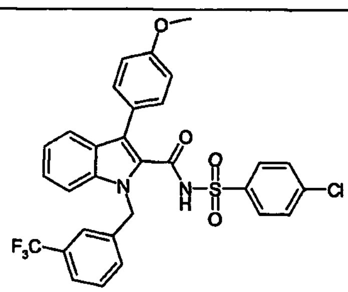
(3-(4-Methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indol-2-yl)-N-(phenylsulfonyl)carboxamide



Benzenesulfonamide (155 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg, 0.50 mmol), and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) were added to a stirred solution of 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indole-2-carboxylic acid (Lit: WO94/14434, 213 mg, 0.50 mmol in dichloromethane (5 mL). The resulting mixture was stirred for 18 h and

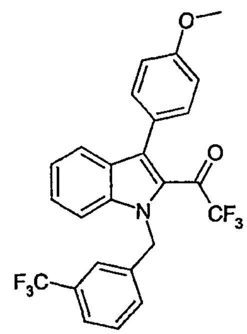
then quenched with hydrochloric acid (1N). The mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic extracts was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified with silica gel flash chromatography using hexane/ethyl acetate (2/1) as the eluant to give a white solid. It was further purified by trituration with diethyl ether to afford (3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indol-2-yl)-N-(phenylsulfonyl) carboxamide as a white solid (220 mg, 78%): mp > 250 °C; MS (electrospray, MH^+) calcd for $C_{30}H_{24}F_3N_2O_4S$ 565.1, found 565.0; ^1H NMR (DMSO-d_6) δ 7.51-8.31 (m, 17 H), 7.03 (br s, 1H), 6.17 (s, 2H), 4.36 (s, 3H).

The following compounds were prepared according to the method of Example 356:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf (TLC)	mp [°C]
357		66	595		
358		33	579		162
359		16	599		166

Example 360

2,2,2-Trifluoro-1-{3-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-1H-indol-2-yl}ethanone



Dess-Martin reagent (39 mg, 0.09 mmol) was added to a stirred solution of 2,2,2-trifluoro-1-(3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indol-2-yl)ethan-1-ol (Example **219**, 40 mg, 0.08 mmol) in dichloromethane (2 mL). The resulting solution was stirred for 2 hours, more oxidant was added, and then the mixture was left stirring for 18 h. The reaction was quenched with a mixed aqueous solution of saturated sodium bicarbonate and saturated sodium thiosulfate (1:1, 10 mL), and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Silica gel flash chromatography using hexane/ethyl acetate (4/1) as the eluant gave 2,2,2-trifluoro-1-(3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]methyl}indol-2-yl)ethan-1-one as an orange oil (27 mg, 70%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.76 (d, 1H), 7.47-7.62 (m, 4H), 7.20-7.45 (m, 5H), 7.05 (d, 2H), 5.76 (s, 2H); MS (MH$^+$) calcd for $C_{25}H_{18}F_6NO_2$: 478., found: 478.

Biological Protocol

The activity of a given compound in binding to PPAR-γ can be assayed routinely according to procedures known in the art. *See, e.g.,* Nichols, *et al.*, Anal. Biochem., 257 (2), (1998), 112-119, 114; Brown, *et al.*, Chem. & Bio., 4 (12), (1997) 909-918. The PPAR-γ binding assay described below was used to determine the PPAR-γ binding activities of the compounds of the invention.

Compounds were tested for their ability to bind to PPARγ using a spin plate assay (gel filtration binding assay). The PPARγ ligand binding domain (LBD) (amino acids 195-475) was expressed in *Escherichia coli* as polyHis-tagged fusion proteins and purified by means of an epitope tag. The LBD (210 ng per well) was then incubated in 96-well microtiter plates for two hours at room temperature with a constant concentration of radioligand (8nM per well) ([^{3}H]BRL 49653) and four concentrations (1 nM, 10 nM, 100nM and 1 μM) of test compound. Each compound was tested in triplicate. Fifty-micloliter aliquots of each well were loaded into each well of an equilibrated 96-well gel filtration plate (Edge Biosystems 31909) and placed on top of a pre-labeled Wallac plate (1450-515). The plates were centrifuged (Beckman GS-6R) at 2500 rpm for 5 minutes, 170 μl Scitisafe® scintillation fluid (Fisher) was added to each well, the plates were sealed, and after 1 hour, were counted in a Wallac MicroBeta counter. The amount of nonspecific binding, as assessed by control wells containing 10 μM of the corresponding unlabeled ligand, was subtracted from each data point. For each compound tested, the data was averaged and plots of ligand concentration versus CPM of radioligand bound were constructed. Apparent IC_{50} values were estimated from nonlinear least-squares fit of the data assuming simple competitive binding.

The compounds of the invention were found to inhibit [^{3}H]BRL 49653 binding at PPAR-γ with an IC_{50} of 10 μM or less. IC_{50} ranges of compounds of the present invention in the PPAR-γ Binding Assay are given in the table below.

Activity of Exemplified Compounds

IC_{50} between 10 nM and 10 μM	**IC_{50} between 100 pM and 9.99 nM**
230	231
233	232
238	234
239	235
241	236
242	237
245	240
246	243
247	244
248	249
251	250

IC_{50} between 10 nM and 10 μM	IC_{50} between 100 pM and 9.99 nM
252	253
254	257
255	258
256	259
267	260
269	261
270	262
274	263
276	264
278	265
279	266
280	268
281	271
282	272
286	273
291	275
292	277
293	283
294	284
295	287
296	288
298	289
300	290
301	297
302	299
303	304
306	305
310	307
318	308
319	311
322	312
323	313

IC_{50} between 10 nM and 10 μM	IC_{50} between 100 pM and 9.99 nM
324	314
325	315
326	316
327	317
328	320
329	321
333	330
337	331
338	332
355	334
358	335
360	336
	339
	340
	341
	342
	343
	344
	345
	346
	347
	348
	349
	350
	351
	352
	353
	354
	356
	357
	359

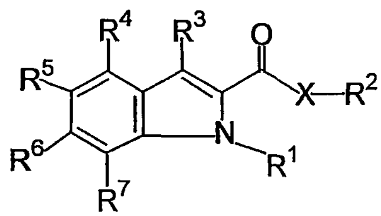
The entire disclosures of all applications, patents and publications cited above are hereby incorporated by reference.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing examples are included by way of illustration only. Accordingly, the scope of the invention is limited only by the scope of the appended claims.

Claims

What is claimed is:

1. A compound according to the general formula (I)



(I)

wherein

R^1

is R^8-R^9;

R^8

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $(CH_2)_tS(=O)_2$, and $(CH_2)_nC(=O)$;

t

is 1-7;

n

is 0-8;

R^9

is selected from phenyl, cycloalkyl of 3-8 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^9 may be substituted with alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, halogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the

perhalo level, or Q-$(CH_2)_nR^{10}$;

Q

is selected from NR^{33}, NH, S and O;

R^{10}

is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

R^{33}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 1-8 carbon atoms and alkynyl of 1-8 carbon atoms;

X

is selected from NR^{33}, NH, O, and S;

R^2

is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, and $(CH_2)_nS(=O)_2R^{11}$;

R^{11}

is selected from aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, with the proviso that R^{11} is not isoxazole,

wherein R^{11} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or

halogen;

R^3

is selected from:

(a) R^{12}-R^{13}, wherein

R^{12}

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, and C(=O), and

R^{13}

is selected from cycloalkyl of 3-7 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{13} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; or

(b) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

all of which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8

carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, or may be spiro fused with cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-8 carbon atoms and 1-2 heteroatoms selected from N, S and O; or

(c) aryl of 5-14 carbon atoms or heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which are substituted with 1-3 of the following:

(i) $Si(CH_3)_3$;

(ii) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, with the proviso that said heterocycloalkenyl is not imidazole;

(iii) $S(=O)_2R^{14}$

wherein R^{14} is selected from cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(iv) R^{15},which combines with R^5 to form a radical of the formula -Y-$(CH_2)_t$-Y-,

wherein Y is selected from NR^{33}, NH, S and O;

(v) $C(=O)R^{16}$,

- wherein R^{16} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and Z-R^{17},

- wherein Z is selected from $(CH_2)_n$, NH, NR^{33}, O and S,

- wherein R^{17} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon

atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(vi) $Z-R^{18}-R^{19}$, wherein:

- R^{18} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms, heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and $(CH_2)_nC(=O)$, and
- R^{19} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, $R^{20}-R^{21}$ and $Z-R^{21}$, and

- Z is as defined above, and
- R^{20} is selected from aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- R^{21} is selected from hydrogen, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

with the proviso that when R^3 is furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl R^3 may be unsubstituted, and

with the further proviso that, (1) when R^3 is aryl or heteroaryl, Z is O or $(CH_2)_n$, R^{18} is $(CH_2)_nC(=O)$, alkyl, aryl or heteroaryl, and R^{19} is hydrogen, halogen, haloalkyl or alkyl, or (2) when R^3 is phenyl or napthyl and R^{16} is alkyl, one of the following applies:

- R^5 is other than hydrogen and R^{23} is other than alkyl or alkenyl,

- X is NH and R^2 is $(CH_2)_nS(=O)_2 R^{11}$,
- R^8 is $(CH_2)_nC(=O)$, $(CH_2)_tS(=O)_2$, alkenyl or alkynyl,
- R^9 is substituted with $Q(CH_2)_nR^{10}$,
- R^7 is other than hydrogen, or
- R^4 is other than hydrogen; and

(d) furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl, which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; or

R^4

is selected from hydrogen and $E-R^{34}-R^{35}$,

wherein

E is selected from NR^{33}, NH, S and O;

R^{34} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

R^{35} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon

atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O; and

R^{33} has the meanings given above;

R^5

(1) is selected from:

(a) hydrogen;

(b) $(CH_2)_qCOOH$

where q is 1-4

(c) $C(=O)R^{22}$,

wherein R^{22} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(d) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(e) $-(CH_2)_n-D-R^{23}$, wherein:

(i) D is selected from NR^{33}, NH, S and O, and

(ii) R^{23} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $C(=O)R^{24}$, and $(CH_2)_mR^{24}$, wherein

- m is 0-4, with the proviso that when R^3 is phenyl or napthyl, Z is O, R^{18} is alkyl and R^{19} is hydrogen, halogen, haloalkyl or alkyl, m is 1-4,

- R^{24} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, C(=O)OH, NHR^{27}-R^{28}, NR^{27}-R^{28}, $(CH_2)_nOR^{27}$-R^{28}, NH-R^{29}-$R^{30}$and R^{29}-R^{30},

- R^{27} is alkyl of 1-8 carbon atoms,

- R^{28} is selected from hydrogen, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

- R^{29} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms, and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

- R^{30} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-

8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and C(=O)OH, or

(2) R^5 combines with R^6 to form a radical of formula -Y-$(CH_2)_t$-Y-,

wherein Y is as defined above;

R^6

is selected from hydrogen, OH, and T-R^{18}-R^{19},

wherein T is selected from NR^{33}, NH, S and O and R^{18}, R^{19} and R^{33} are as defined above;

R^7

is selected from hydrogen, C(=O)R^{22}, $(CH_2)_n$-D-R^{23}, and R^{31}-R^{32},

wherein D, R^{22} and R^{23} are as defined above, and

R^{31}

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and C(=O), and

R^{32}

is selected from aryl of 5-14 carbon atoms, heteroaryl of 3-1 1 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{32} may be substituted with alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon

atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein one of R^4, R^5, R^6 and R^7 is hydrogen, and pharmaceutically acceptable salts thereof.

3. The compound of claim 2, wherein R^4 and R^7 are hydrogen, and pharmaceutically acceptable salts thereof.

4. The compound of claim 3, wherein

R^5

is selected from $(CH_2)_qCOOH$, $C(=O)R^{22}$, $(CH_2)_nD\text{-}R^{23}$, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloakenyl of 3-9 carbon atoms and 1-2 heteroatoms selected from N, S and O, or R^5 combines with R^6 or R^3 to form a radical of the formula $-Y-(CH_2)_t-Y-$;

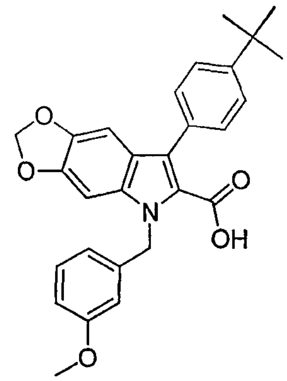
R^6

is selected from OH, $T\text{-}R^{18}\text{-}R^{19}$ or combines with R^5 to form a radical of the formula $-Y-(CH_2)_t-Y-$;

and pharmaceutically acceptable salts thereof.

5. The compound of claim 4, wherein R^5 combines with R^6 to form a radical of the formula $-Y-(CH_2)_t-Y-$; and pharmaceutically acceptable salts thereof.

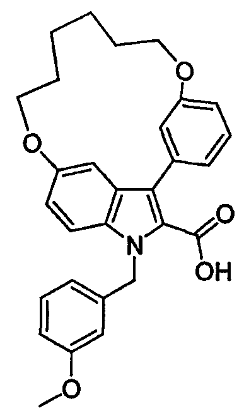
6. The compound of claim 5:



and pharmaceutically acceptable salts thereof.

7. The compound of claim 4, wherein R^5 combines with R^3 to form a radical of the formula $-Y-(CH_2)_t-Y-$; and pharmaceutically acceptable salts thereof.

8. The compound of claim 7:



and pharmaceutically acceptable salts thereof.

9. The compound of claim 4, wherein

R^5

is selected from $(CH_2)_qCOOH$, $C(=O)R^{22}$, $(CH_2)_nD-R^{23}$, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloakenyl of 3-9 carbon atoms and 1-2 heteroatoms selected from N, S and O; and

R^6

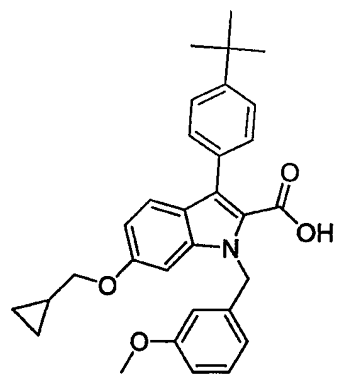
is selected from OH and T-R^{18}-R^{19};

and pharmaceutically acceptable salts thereof.

10. The compound of claim 3, wherein R^5 is hydrogen; and pharmaceutically acceptable salts thereof.

11. The compound of claim 10, wherein R^6 is selected from OH and T-R^{18}-R^{19}.

12. The compound of claim 11:



and pharmaceutically acceptable salts thereof.

13. The compound of claim 3, wherein R^6 is hydrogen; and pharmaceutically acceptable salts thereof.

14. The compound of claim 13, wherein

R^5

is selected from $(CH_2)_qCOOH$, $C(=O)R^{22}$, $(CH_2)_nD$-R^{23}, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloakenyl of 3-9 carbon atoms and 1-2 heteroatoms selected from N, S and O;

and pharmaceutically acceptable salts thereof.

15. The compound of claim 14, wherein R^5 is selected from $(CH_2)_nD\text{-}R^{23}$, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloakenyl of 3-9 carbon atoms and 1-2 heteroatoms selected from N, S and O; and pharmaceutically acceptable salts thereof.

16. The compound of claim 15, wherein

D is selected from O, NR^{33} and NH;

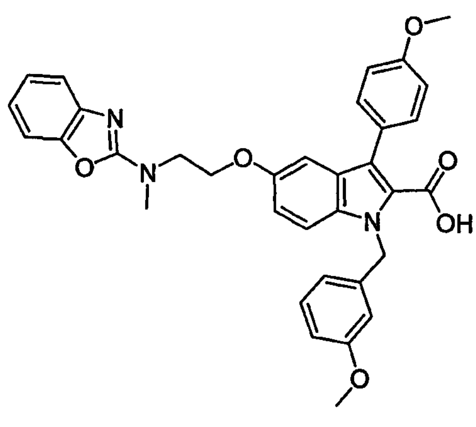
n is 0-2;

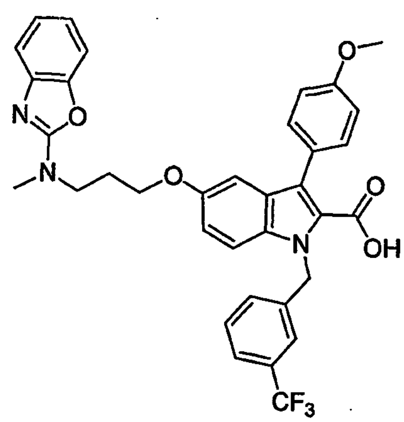
R^{23} is selected from alkyl, alkenyl, $C(=O)R^{24}$ and $(CH_2)_mR^{24}$;

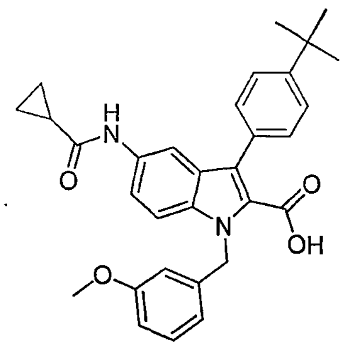
R^{24} is selected from cycloalkyl of 3-9 carbon atoms, COOH, $NR^{27}\text{-}R^{28}$, $NH\text{-}R^{27}\text{-}R^{28}$, $C(=O)R^{29}\text{-}R^{30}$ and $O\text{-}R^{27}\text{-}R^{28}$;

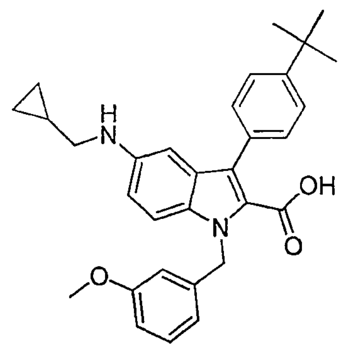
and pharmaceutically acceptable salts thereof.

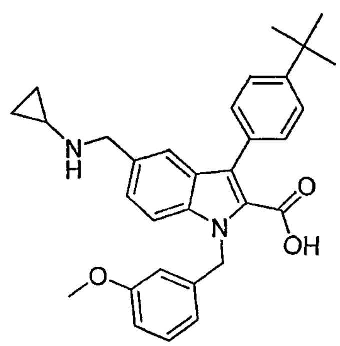
17. The compound of claim 16 selected from:

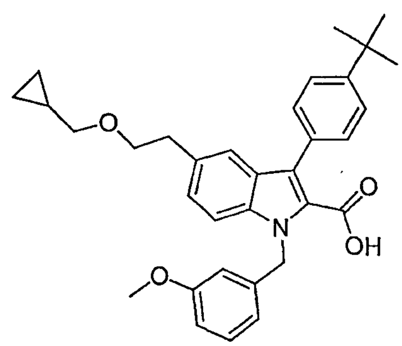


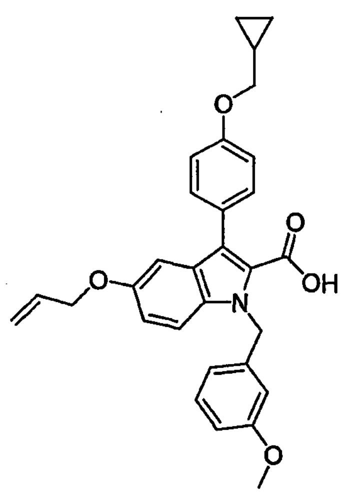


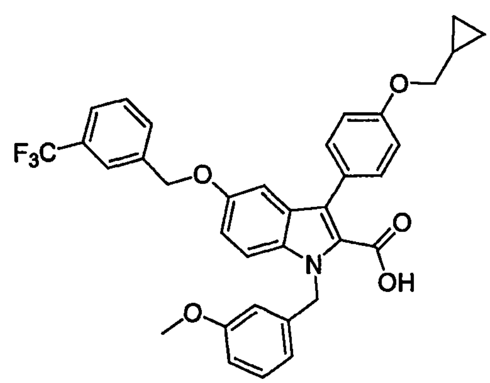


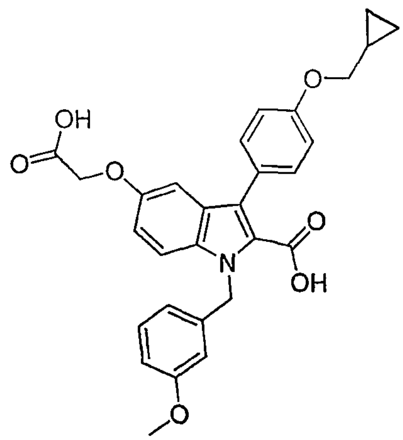


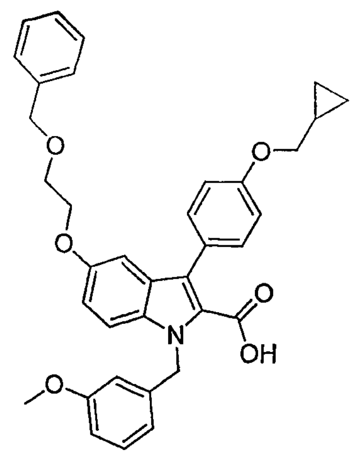


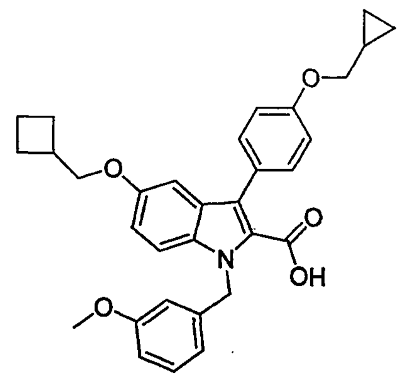


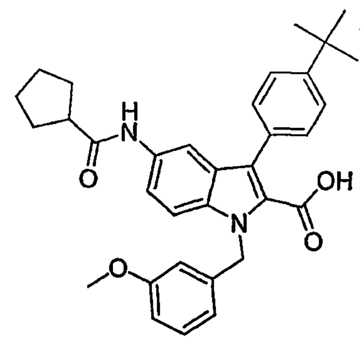


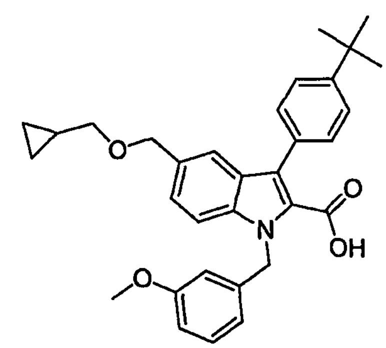


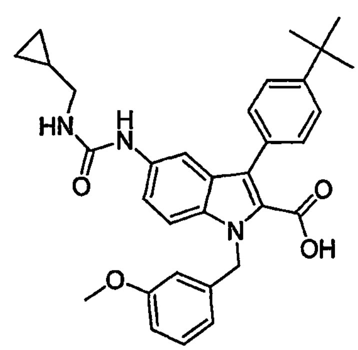


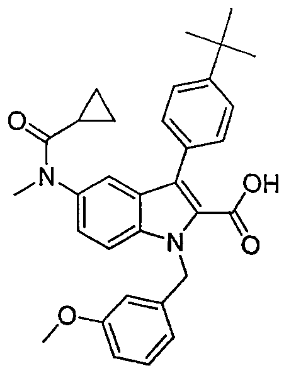


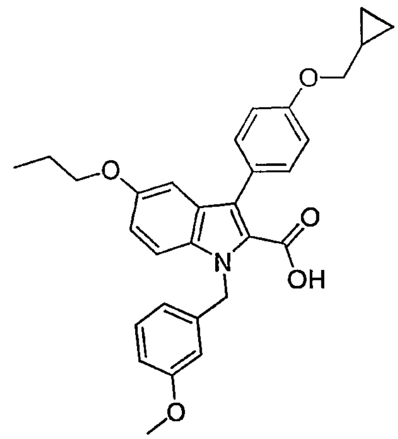


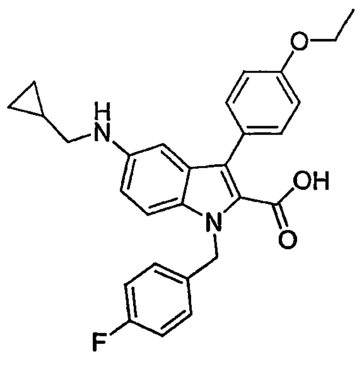


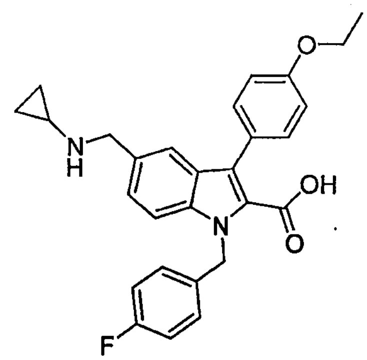


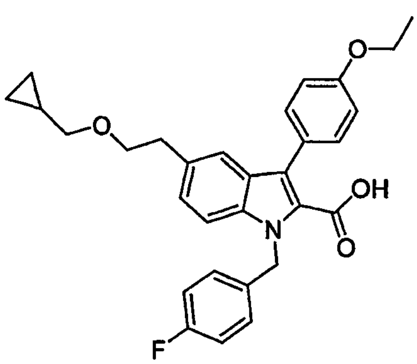


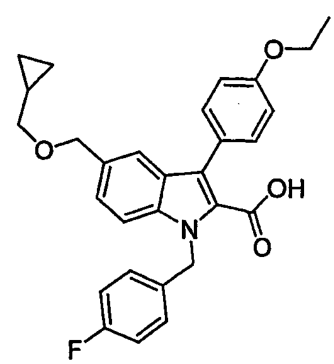


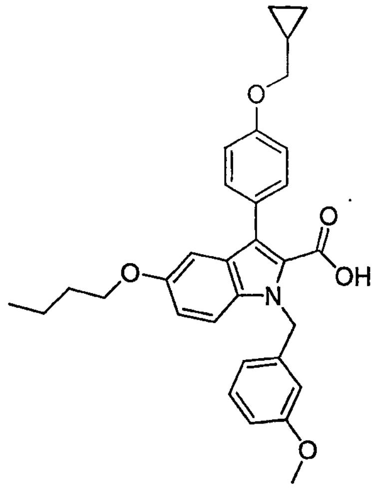


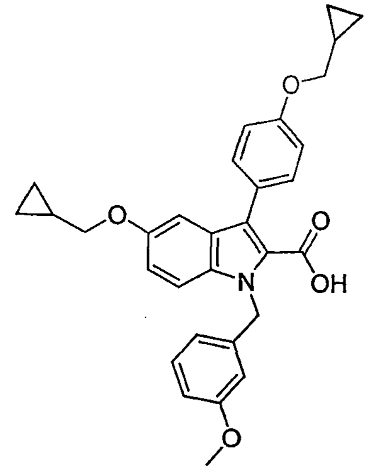


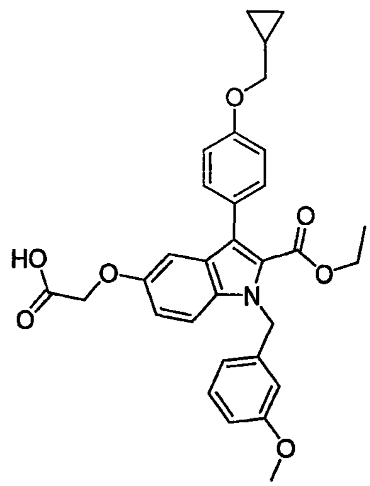


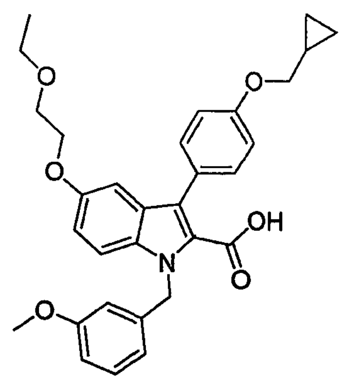


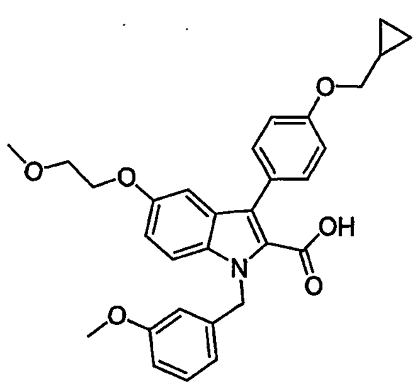


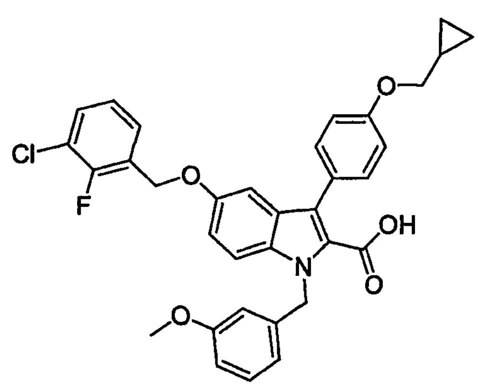

O
O
OH
N
O
O

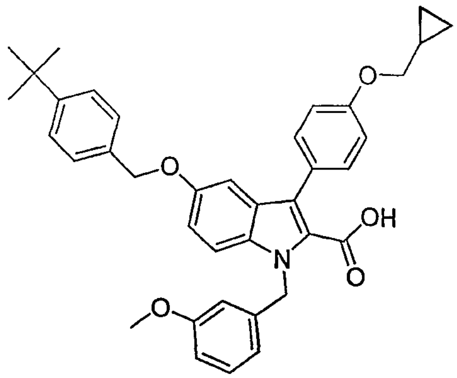

O
O
O
N
OH
O

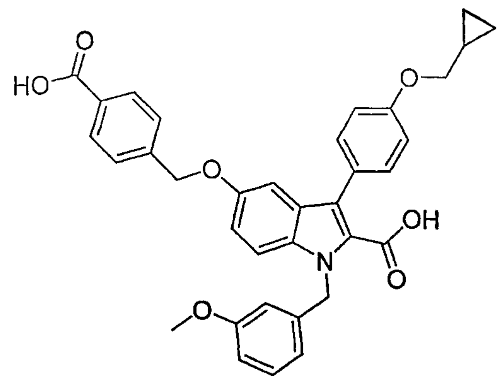

O
O
HO
O
O
N
O
O
O

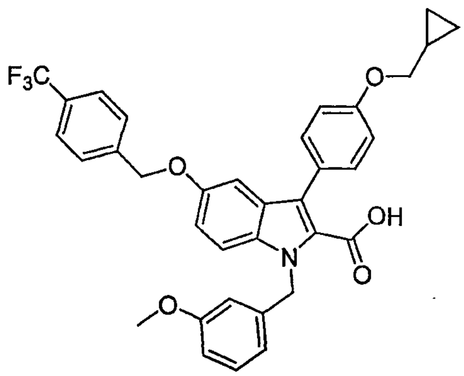

O
O
O
OH
N
O
O

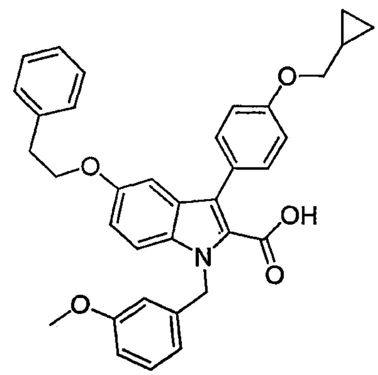

O
O
O
OH
N
O
O

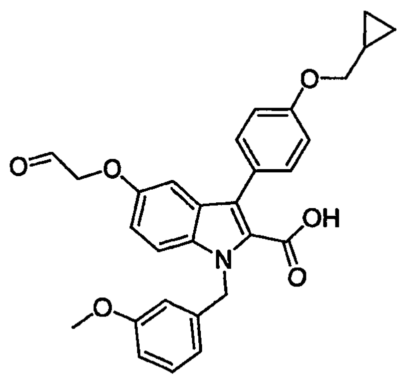

O
Cl
F
O
OH
N
O
O

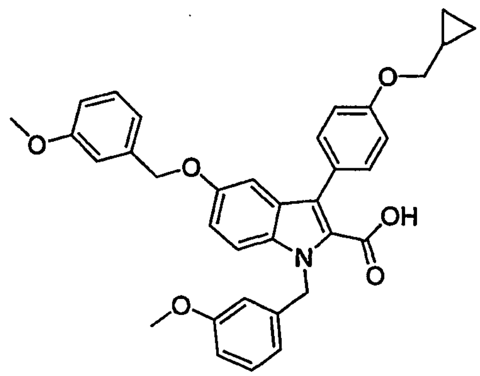


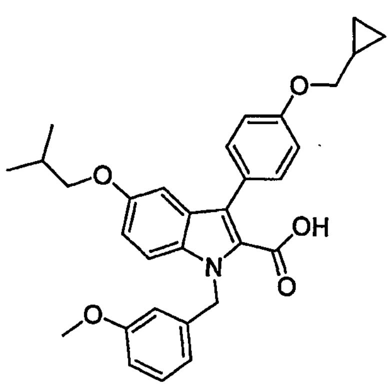


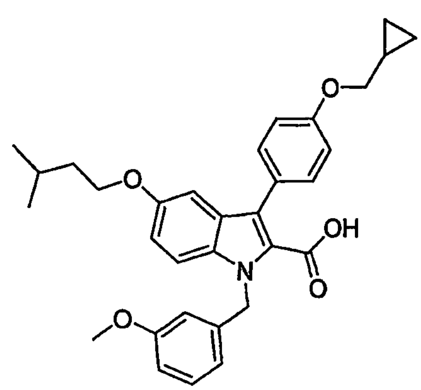












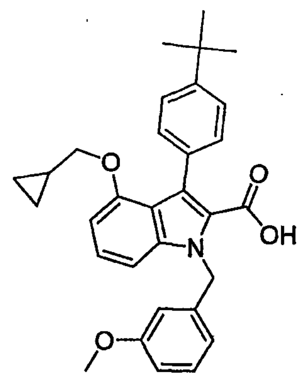
and pharmaceutically acceptable salts thereof.

18. The compound of claim 2, wherein R^5, R^6 and R^7 are hydrogen; and pharmaceutically acceptable salts thereof.

19. The compound of claim 18, wherein R^4 is E-R^{34}-R^{35}; and pharmaceutically acceptable salts thereof.

20. The compound of claim 19, wherein E is O, R^{34} is alkyl and R^{35} is cylcoalkyl; and pharmaceutically acceptable salts thereof.

21. The compound of claim 20:



and pharmaceutically acceptable salts thereof.

22. The compound of claim 2, wherein R^4, R^5 and R^6 are hydrogen; and pharmaceutically acceptable salts thereof.

23. The compound of claim 22, wherein R^7 is selected from C(=O)R^{22}, $(CH_2)_n$D-R^{23}, and R^{31}-R^{32}; and pharmaceutically acceptable salts thereof.

24. The compound of claim 23, wherein

D is selected from O, NH and NR^{33};

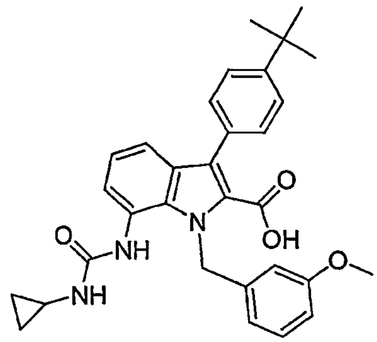
n is 0-2;

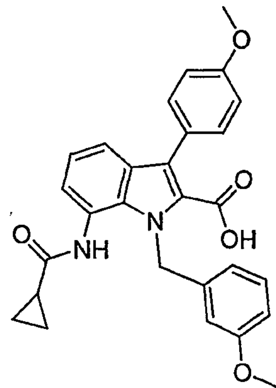
R^{23} is selected from alkyl of 1-8 carbon atoms, C(=O)R^{24}, and $(CH_2)_mR^{24}$;

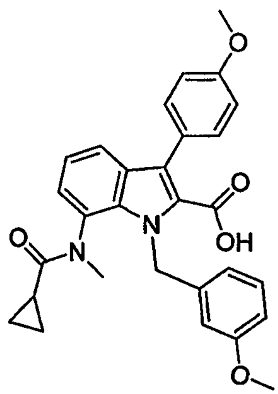
R^{24} is selected from $C(=O)R^{29}-R^{30}$, $NHR^{29}-R^{30}$ and $NR^{27}-R^{28}$;

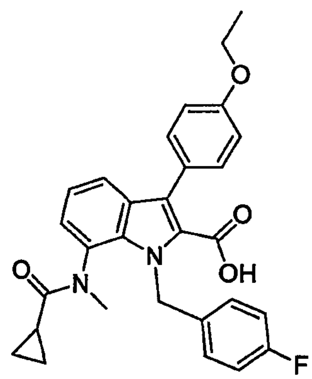
and pharmaceutically acceptable salts thereof.

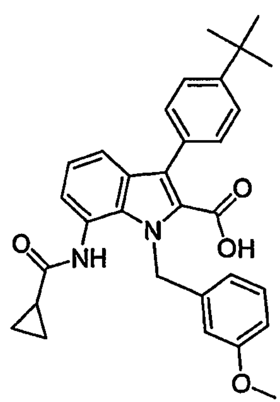
25. The compound of claim 24 selected from:

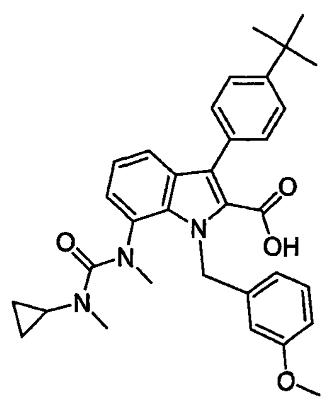












and pharmaceutically acceptable salts thereof.

26. The compound of claim 2, wherein all of R^4, R^5, R^6 and R^7 are hydrogen; and pharmaceutically acceptable salts thereof.

27. The compound of claim 26, wherein

R^8

is selected from alkyl, alkenyl and $(CH_2)_nC(=O)$;

R^9

is selected from phenyl and cylcoalkyl;

X

is selected from O, NH and NR^{33};

R^2

is selected from H and $(CH_2)_nS(=O)_2R^{11}$;

R^3

is selected from

(a) R^{12}-R^{13},

(b) heterocycloalkyl or heterocycloalkenyl,

(c) aryl or heteroaryl, and

(d) furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl, which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to

the perhalo level, or halogen;

and pharmaceutically acceptable salts thereof.

28. The compound of claim 27, wherein

R^{12}

is selected from alkyl, alkenyl and C(=O);

R^{13}

is selected from cycloalkyl, heterocylcoalkyl and heterocycloakenyl;

R^3

is selected from:

(a) phenyl and furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl, which may be substituted with:

(i) $C(=O)R^{16}$, wherein R^{16} is selected from alkyl and QR^{17}, Q is selected from O, NH and NR^{33}, and R^{17} is cycloalkyl,

(ii) $Z\text{-}R^{18}\text{-}R^{19}$, wherein Z is selected from O, NH, NR^{33}, S and $(CH_2)_n$, R^{18} is selected from C(=O), alkyl, cycloalkyl and heterocycloalkyl, R^{19} is selected from hydrogen, cycloalkyl, heterocycloalkyl, $Q\text{-}R^{21}$ and $R^{20}\text{-}R^{21}$, Q is selected from O, NH and NR^{33}, R^{20} is selected from aryl and heteroaryl, and R^{21} is selected from hydrogen, heterocycloalkyl and cycloalkyl;

(iii) cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl;

(b) furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl,

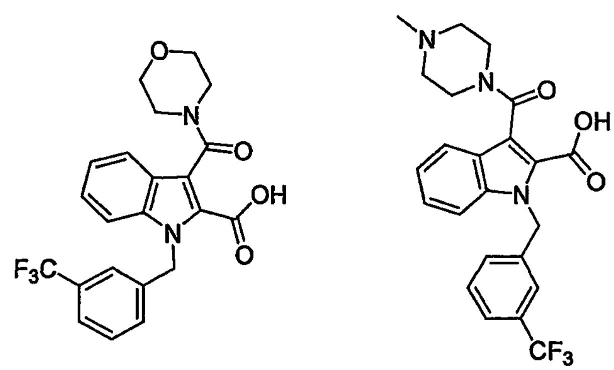
benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl, which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; and

(c) cycloalkyl and heterocycloalkenyl;

and pharmaceutically acceptable salts thereof.

29. The compound of claim 28, wherein R^{12} is C(=O); and pharmaceutically acceptable salts thereof.

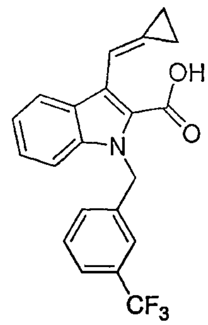
30. The compound of claim 29, selected from:

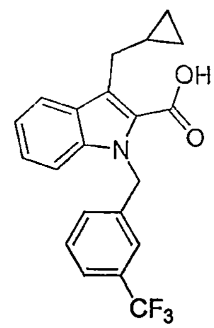


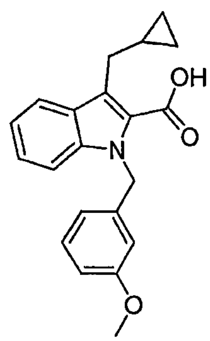
and pharmaceutically acceptable salts thereof.

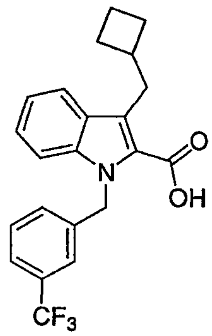
31. The compound of claim 28, wherein R^{12} is selected from alkyl and alkenyl; and pharmaceutically acceptable salts thereof.

32. The compound of claim 31, selected from:





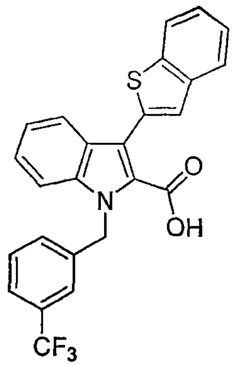


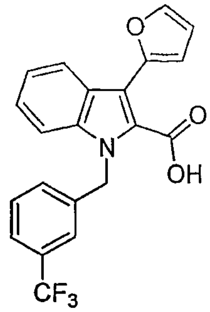


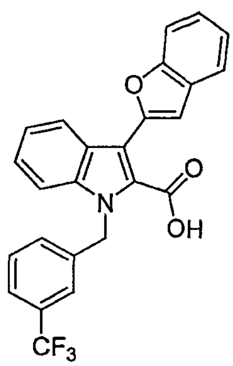
and pharmaceutically acceptable salts thereof.

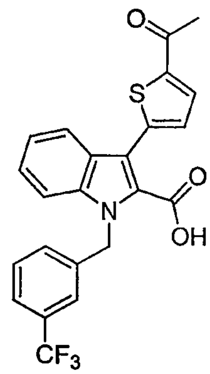
33. The compound of claim 28, wherein R^3 is selected from furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl, which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; and pharmaceutically acceptable salts thereof.

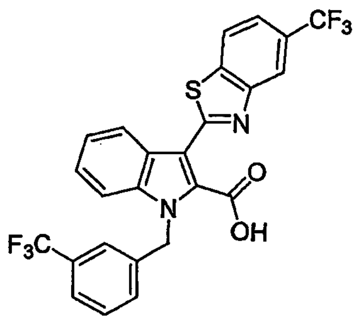
34. The compound of claim 33, selected from:

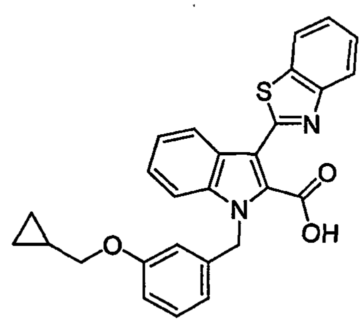


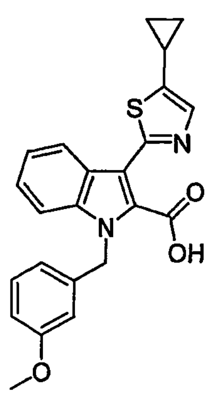


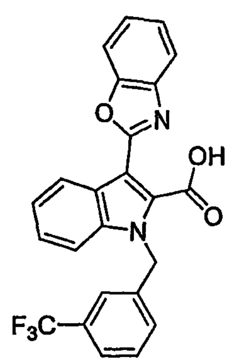


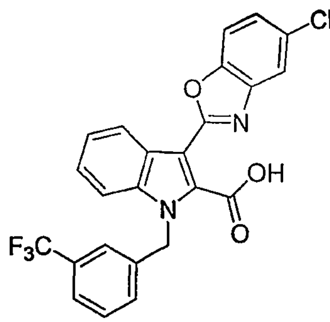


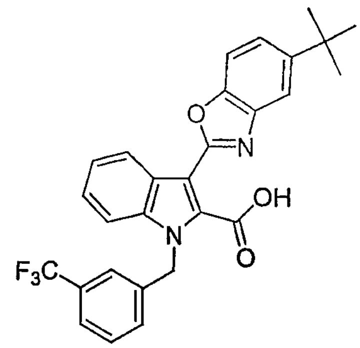


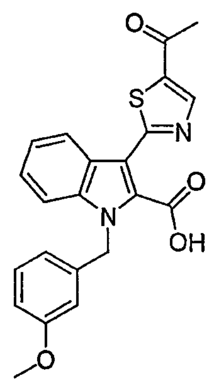










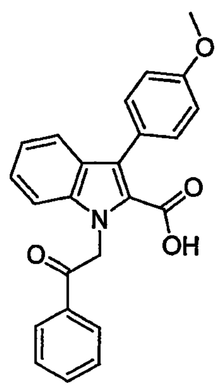


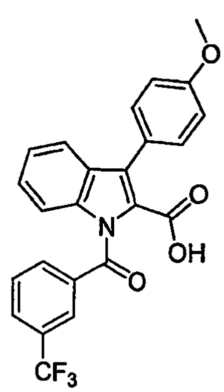
and pharmaceutically acceptable salts thereof.

35. The compound of claim 28, wherein R^3 is phenyl; and pharmaceutically acceptable salts thereof.

36. The compound of claim 35, wherein R^8 is $(CH_2)_nC(=O)$; and pharmaceutically acceptable salts thereof.

37. The compound of claim 36, selected from:





and pharmaceutically acceptable salts thereof

38. The compound of claim 35, wherein

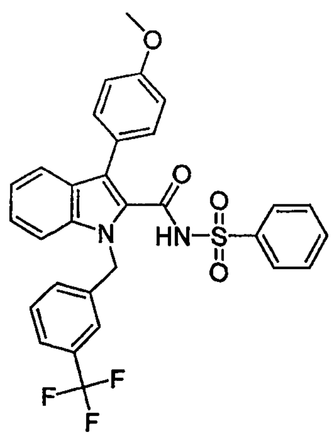
R^8 is selected from alkyl and alkenyl;

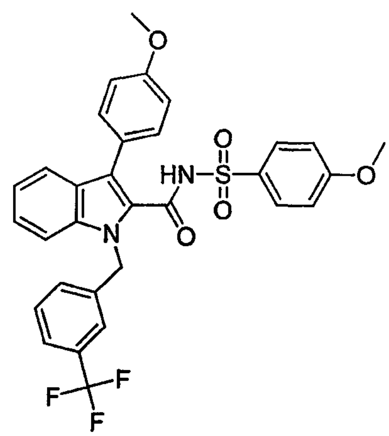
X is selected NH and NR^{33};

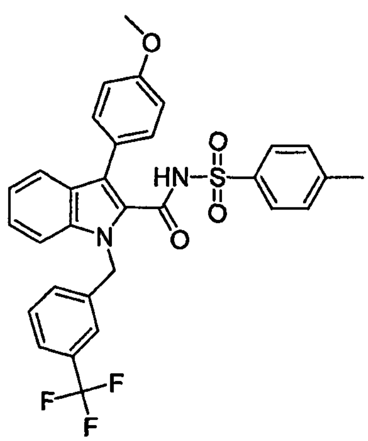
R^2 is $(CH_2)_nS(=O)_2R^{11}$; and

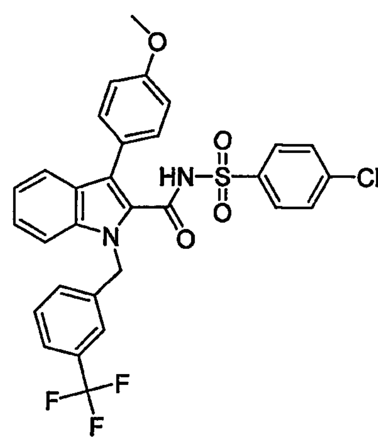
pharmaceutically acceptable salts thereof.

39. The compound of claim 38 selected from:









and pharmaceutically acceptable salts thereof.

40. The compound of claim 35, wherein

R^8 is selected from alkyl or alkenyl;

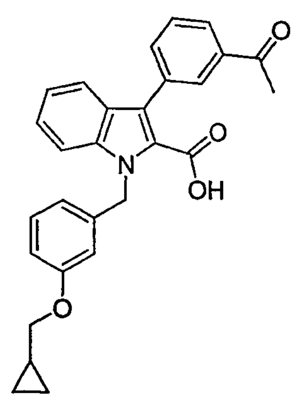
X is O;

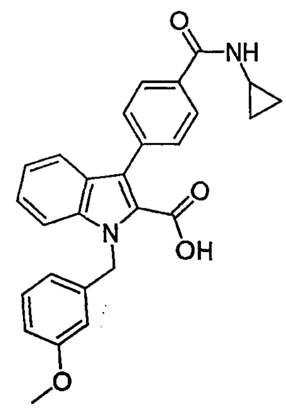
R^2 is hydrogen;

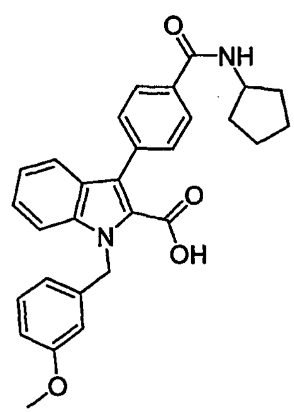
R^3 is phenyl substituted with $C(=O)R^{16}$;

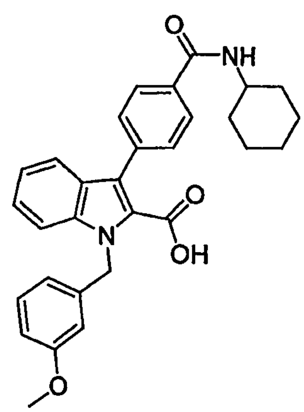
and pharmaceutically acceptable salts thereof.

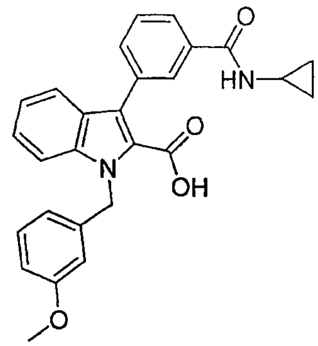
41. The compound of claim 40, selected from:

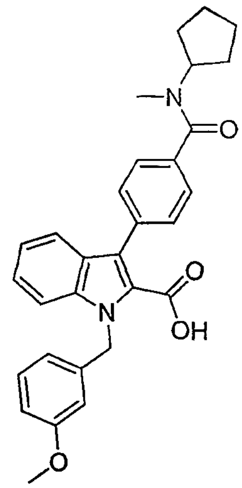


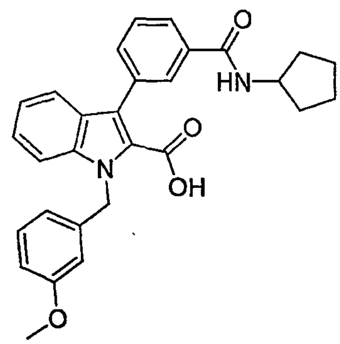












and pharmaceutically acceptable salts thereof.

42. The compound of claim 35, wherein

R^8 is selected from alkyl and alkenyl;

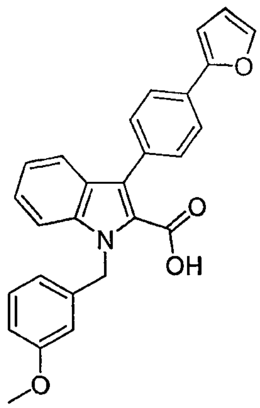
X is O;

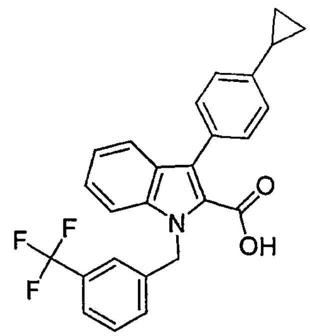
R^2 is hydrogen;

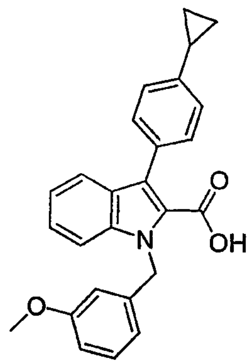
R^3 is phenyl substituted with cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloakenyl;

and pharmaceutically acceptable salts thereof.

43. The compound of claim 42, selected from:







and pharmaceutically acceptable salts thereof.

44. The compound of claim 35, wherein

R^8 is selected from alkyl and alkenyl;

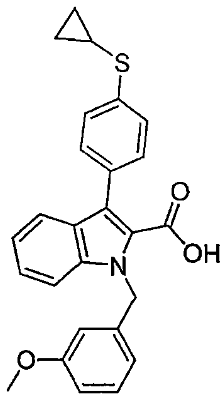
X is O;

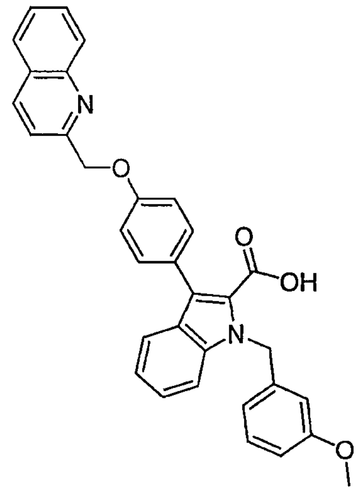
R^2 is hydrogen;

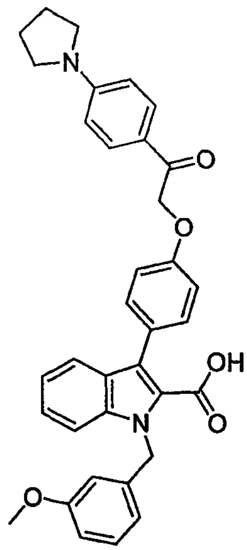
R^3 is phenyl substituted with Z-R^{18}-R^{19};

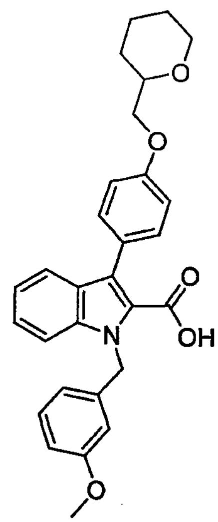
and pharmaceutically acceptable salts thereof.

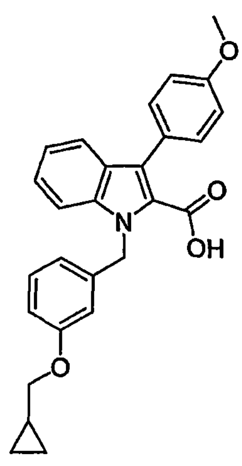
45. The compound of claim 44, selected from:

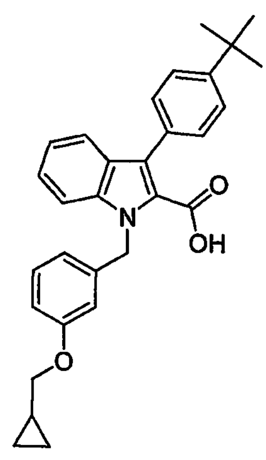

S
O
OH
N
O

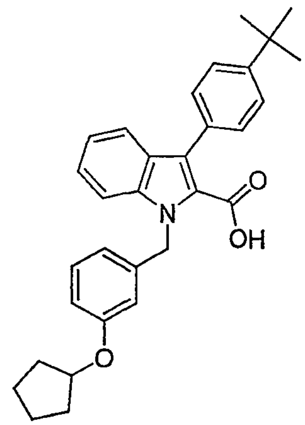

N
O
O
OH
N
O


N
O
O
OH
N
O
O

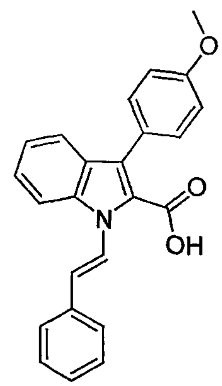

O
O
O
N
OH
O


O
O
N
OH
O

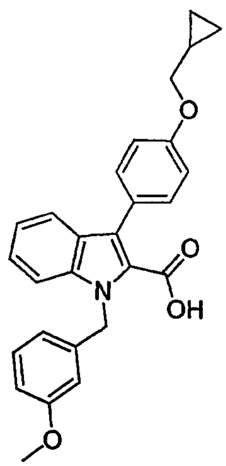

O
N
OH
O



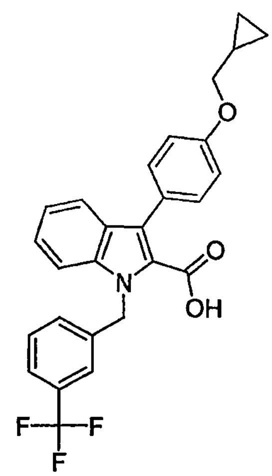
N
O
OH
O



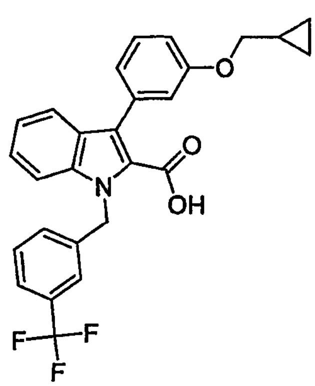
O
N
O
OH



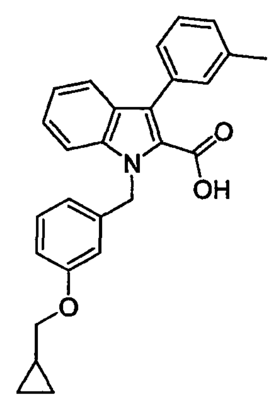
O
N
O
OH
O



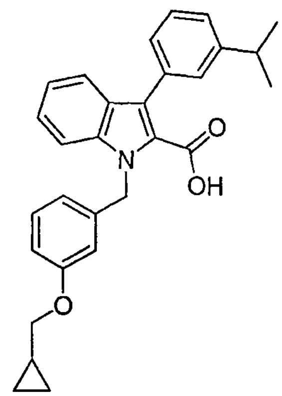
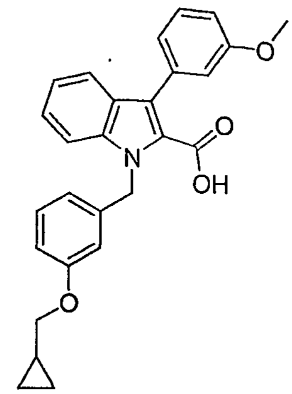
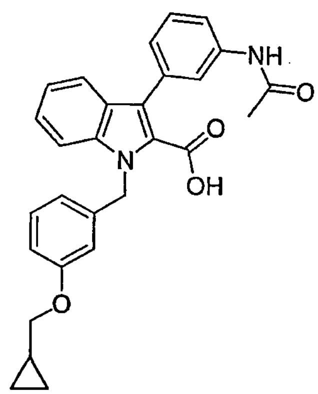
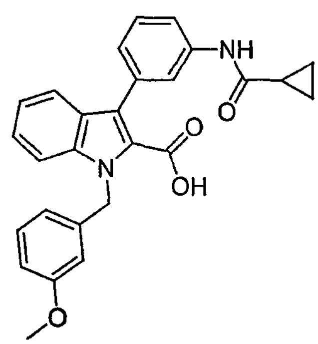
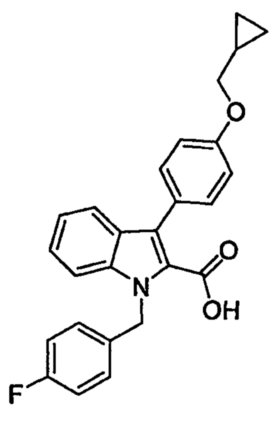
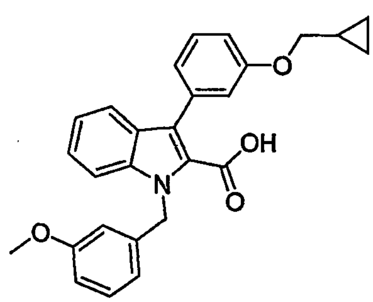
O
N
O
OH
F
F
F

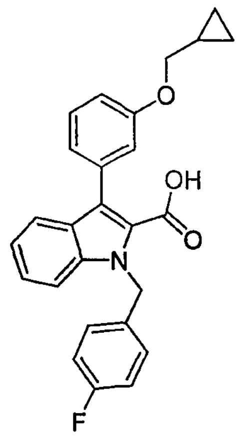


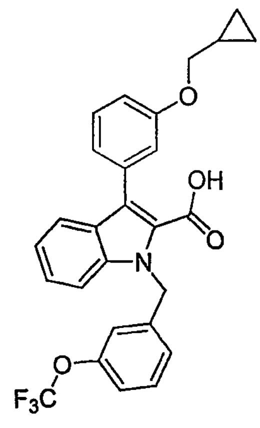
O
N
O
OH
F
F
F

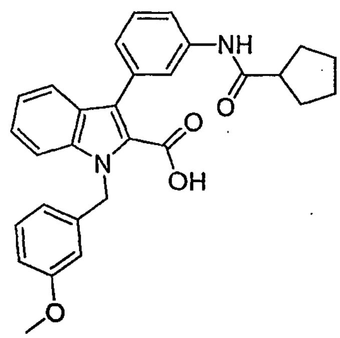


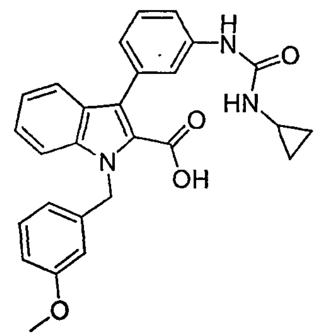
N
O
OH
O

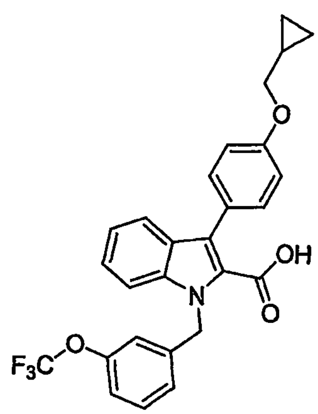







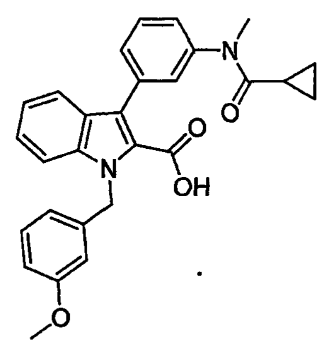


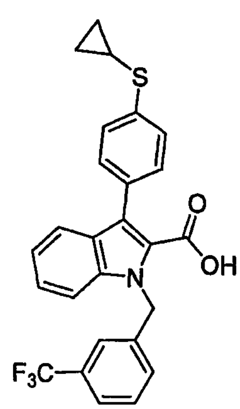








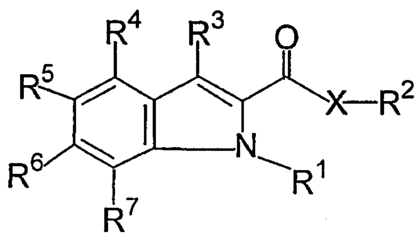




and pharmaceutically acceptable salts thereof.

46. Pharmaceutical compositions comprising a compound according to claim 1, 2, 3, 4, 9, 10, 11, 13, 14, 18, 19, 22, 23, 26, 27, 28, 29, 31, 33, 35, 38, 40, 42, or 44 and a pharmaceutically acceptable carrier.

47. A method of treating or preventing a PPAR-γ mediated disease or condition, comprising administering to a mammal a compound according to formula IIa



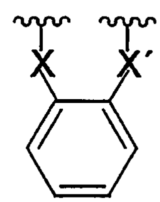
(IIa)

wherein

R^1

(1) is selected from hydrogen and R^8-R^9, or

(2) combines with R^7 to form a radical of the formula



R^8

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $(CH_2)_nS(=O)_2$ and $(CH_2)_nC(=O)$;

R^9

is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S

and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

wherein R^9 may be substitituted with alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, halogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or X-$(CH_2)_nCH_3R^{10}$,

R^{10}

is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

X and X′

are each independently selected from NH, NR^{33}, $(CH_2)_n$, O and S;

n

is a number from 0-8;

R^{33}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms and alkynyl of 2-8 carbon atoms;

R^2

is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, $NHS(=O)_2R^{11}$, and $(CH_2)_nS(=O)_2R^{11}$;

R^{11}

is selected from aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{11} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to

the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

R^3

is selected from:

(a) hydrogen,

(b) R^{12}-R^{13}, wherein

R^{12}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and $(CH_2)_nC(=O)$,

R^{13}

is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{13} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

(c) cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, all of which may be:

(i) substituted with aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2

heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and $C(=O)(CH_2)_nCH_3$, or

(ii) fused with a spiro ring of 1-6 carbon atoms, or

(iii) fused with an aryl of 5-14 carbon atoms or a heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, either of which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

(d) aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, either of which may be substituted with:

(i) $-Si(CH_3)_3$;

(ii) $S(=O)_2R^{14}$,

wherein R^{14} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(iii) R^{15}, which combines with R^5 to form a radical of the formula $-Y-(CH_2)_n-Y-$,

wherein Y and n are as defined above;

(iv) $C(=O)R^{16}$,

- wherein R^{16} is selected from alkyl of 1-8 carbon atoms and $X-R^{17}$

- wherein R^{17} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- wherein X is as defined above;

(v) $X\text{-}R^{18}\text{-}R^{19}$

- R^{18} is selected from alkyl of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,
- R^{19} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, $R^{20}\text{-}R^{21}$ and $X\text{-}R^{21}$,
- X is as defined above,

- R^{20} is aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- R^{21} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

R^4

is selected from hydrogen and X-R^{18}-R^{19},

wherein X, R^{18} and R^{19} have the meanings given above;

R^5

(1) is selected from:

(a) hydrogen;

(b) R^{12}-R^{13},

wherein R^{12} and R^{13} are as defined above,

(c) C(=O)R^{22}, wherein

R^{22} is selected from alkyl of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(d) alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon

atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(e) $-(CH_2)_n$-Y-R^{23}, wherein:

(i) Y and n are as defined above,

(ii) R^{23} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $C(=O)R^{24}$, $(CH_2)_nR^{24}$, and R^{25}-R^{26}, wherein

- R^{25} is alkyl of 1-8 carbon atoms,
- R^{26} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,
- R^{24} is selected from cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, C(=O)OH, NHR^{27}-R^{28}, NR^{27}-R^{28}, $NR^{33}R^{27}$-R^{28}, $(CH_2)_nR^{27}$-R^{28}, and R^{29}-R^{30},
- R^{27} is alkyl of 1-8 carbon atoms,
- R^{28} is selected from hydrogen, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, all of which, with the exception of hydrogen, may be fused with aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected N, S and O,

- R^{29} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- R^{30} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(2) combines with R^6 to form a radical of the formula $-Y-(CH_2)_n-Y-$,

wherein Y and n have the meanings given above;

R^6

is selected from hydrogen, OH and $X-R^{18}-R^{19}$,

wherein X, R^{18} and R^{19} have the meanings give above

R^7

is selected from hydrogen, $C(=O)R^{22}$, $(CH_2)_n-Y-R^{23}$, and $R^{12}-R^{13}$,

wherein R^{22}, R^{23}, R^{12}, R^{13}, Y and n have the meanings give above;

and pharmaceutically acceptable salts thereof.

48. A method of treating or preventing a PPAR-γ mediated disease or condition, comprising administering to a mammal a compound according to claim 1, 2, 3, 4, 9, 10, 11, 13, 14, 18, 19, 22, 23, 26, 27, 28, 29, 31, 33, 35, 38, 40, 42, or 44.

49. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is osteoporosis or osteopenia.

50. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is a PPAR-γ mediated cancer.

51. The method of claim 50, wherein said PPAR-γ mediated cancer is selected from breast, prostate, lung, liposacrcoma and colon cancer.

52. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is selected from hyperglycemia, type 1 diabetes, type 2 diabetes, syndrome X and insulin resistance.

53. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is selected from dyslipidemia, hypertriglyceridemia, diabetic dyslipidemia, hyperlipidemia, and hypercholesteremia.

54. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is an inflammatory condition.

55. The method of claim 54, wherein said inflammatory condition is selected from atherosclerosis, inflammatory bowel disease, Alzheimer's disease and rheumatoid arthritis.

56. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is hypertension.

57. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is obesity.

58. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is a skin disorder.

59. The method of claim 58, wherein said skin disorder is selected from acne, psoriasis, dermatitis, eczema, and keratosis.

60. The method of claim 47 or 48, wherein said PPAR-γ mediated disease or condition is lupus erythematosus.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/42644

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/42 C07D491/04 C07D413/12 C07D409/04 C07D405/04
C07D417/04 C07D405/10 C07D401/12 C07D405/12 A61K31/404
A61K31/428 A61K31/423 A61K31/343 //(C07D491/04,317:00,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ACHAB, SAIED ET AL: "An expeditious synthesis of structural analogs of the marine cytotoxic agents grossularines-1 and -2" TETRAHEDRON LETT. (1995), 36(15), 2615-18 , XP001057893 see compound 15 and 6	1-3,10, 13,18, 22,26
X	GABRIELYAN, G. E. ET AL: "Indole derivatives. XXXVII. Synthesis of indole compounds containing a furan ring" ARM. KHIM. ZH. (1973), 26(9), 768-74 , XP001061897 see compound XI and X	1-3, 13-16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2002	27/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/42644

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06 145150 A (KYOWA HAKKO KOGYO KK, JAPAN) 24 May 1994 (1994-05-24) the whole document ---	1-60
A	MEDERSKI W W K R ET AL: "2, ENDOTHELIN ANTAGONISTS: EVALUATION OF 2,1,3-BENZOTHIADIAZOLE AS A METHYLENDIOXYPHENYL BIOISOSTER" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 1, 1998, pages 17-22, XP001057891 ISSN: 0960-894X see page 19 and Table 2 the whole document --- -/--	1-60

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 449 196 A (TAKEDA CHEMICAL INDUSTRIES LTD) 2 October 1991 (1991-10-02) the whole document ---	1-60
X	WO 94 14434 A (SMITHKLINE BEECHAM CORP ;ELLIOTT JOHN DUNCAN (US); LEBER JACK DALE) 7 July 1994 (1994-07-07) see especially formula I definitions of R2 and R1 the whole document ---	1-46
X	WO 97 19077 A (MERCK PATENT GMBH ;MEDERSKI WERNER (DE); OSSWALD MATHIAS (DE); DOR) 29 May 1997 (1997-05-29) see formula II ---	1-46
A	US 6 090 839 A (ADAMS ALAN D ET AL) 18 July 2000 (2000-07-18) the whole document ---	1-60
A	WO 00 23425 A (NOVONORDISK AS ;REDDY RESEARCH FOUNDATION (IN)) 27 April 2000 (2000-04-27) the whole document ---	1-60
Y	EP 0 782 989 A (KYOWA HAKKO KOGYO KK) 9 July 1997 (1997-07-09) the whole document -----	1-60

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.:
1-4,7,9-11,13-16,18-20,22-24,26-29,31,33,35-3,38,40,42,44,46 (partly)

Present claims
1-4,7,9-11,13-16,18-20,22-24,26-29,31,33,35-36,38,40,42,44,,46 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the specific compounds of the claims and examples and a reasonable generaliation thereof, such that R1 is CH2Ph (optionally substituted)

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/42644

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
JP 6145150	A	24-05-1994	NONE			
EP 0449196	A	02-10-1991	CA	2038925	A1	27-09-1991
			EP	0449196	A2	02-10-1991
			JP	4211651	A	03-08-1992
			US	5296499	A	22-03-1994
WO 9414434	A	07-07-1994	AU	5873594	A	19-07-1994
			CN	1096513	A	21-12-1994
			EP	0676959	A1	18-10-1995
			JP	8504826	T	28-05-1996
			MX	9400071	A1	29-07-1994
			WO	9414434	A1	07-07-1994
			ZA	9309516	A	06-06-1994
WO 9719077	A	29-05-1997	DE	19543639	A1	28-05-1997
			AU	7694496	A	11-06-1997
			WO	9719077	A1	29-05-1997
			EP	0863898	A1	16-09-1998
			ZA	9609775	A	21-05-1998
US 6090839	A	18-07-2000	AU	1856997	A	22-08-1997
			AU	719663	B2	11-05-2000
			AU	5615298	A	17-07-1998
			EP	0948327	A1	13-10-1999
			JP	2001511767	T	14-08-2001
			WO	9728149	A1	07-08-1997
			WO	9827974	A1	02-07-1998
			US	6160000	A	12-12-2000
WO 0023425	A	27-04-2000	AU	6190299	A	08-05-2000
			WO	0023425	A1	27-04-2000
			EP	1123279	A1	16-08-2001
EP 0782989	A	09-07-1997	AU	6370196	A	18-02-1997
			EP	0782989	A1	09-07-1997
			CA	2199978	A1	06-02-1997
			WO	9703965	A1	06-02-1997
			US	5891902	A	06-04-1999